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TOXICOLOGICAL PROFILE FOR TETRACHLOROETHYLENE

Syracuse Research Corporation
Syracuse, NY

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Toxicological Profile for

TETRACHLOROETHYLENE

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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TOXICOLOGICAL PROFILE FOR TETRACHLOROETHYLENE

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FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The list of the 100 most significant hazardous substances was published in the *Federal Register* on April 17, 1987.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> "(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.
>
> (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that describes a hazardous substance's toxicological properties. Other literature is presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Research gaps in toxicologic and health effects information are described in the profile. Research gaps that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents in response to public comments and as additional data become available; therefore, we encourage comment that will make the toxicological profile series of the greatest use.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

James O. Mason

James O. Mason, M.D., Dr. P.H.
Assistant Surgeon General
Administrator, ATSDR

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1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS TETRACHLOROETHYLENE?

Tetrachloroethylene is a man-made substance widely used for dry cleaning fabrics and textiles and for metal-degreasing operations. It is also used as a starting material (building block) for the production of other man-made chemicals. Other names that may be used for tetrachloroethylene include perchloroethylene, perc, PCE, perclene, and perchlor. Although tetrachloroethylene is a liquid at room temperature, some of the liquid can be expected to evaporate into the air producing an ether-like odor; evaporation increases as temperature increases.

1.2 HOW MIGHT I BE EXPOSED TO TETRACHLOROETHYLENE?

Humans can be exposed to tetrachloroethylene from environmental, consumer product, and occupational sources. Common environmental levels of tetrachloroethylene (often called background levels) are usually several thousand times lower than levels found in some workplaces. Background levels found in the air we breathe and in the food and water we consume probably result from evaporation from industrial or dry-cleaning operations or from releases from areas where chemical wastes are stored. Tetrachloroethylene has been found in at least 330 of the 1,117 National Priorities List (NPL) hazardous waste sites.

In general, tetrachloroethylene levels in air are higher in urban and industrialized areas than in more rural or remote areas. Higher-than-background concentrations of tetrachloroethylene have occasionally been measured in air close to chemical waste sites and in water taken from nearby wells.

Exposure to tetrachloroethylene may also occur from some consumer products. Products that may contain tetrachloroethylene include auto brake quieters and cleaners, suede protectors, water repellants, silicone lubricants, belt lubricants and dressings, specialized aerosol cleaners, ignition wire driers, fabric finishers, spot removers, adhesives, and wood cleaners. Although uncommon, small amounts of tetrachloroethylene have been found in food.

The levels of tetrachloroethylene in air in dry-cleaning shops, textile and chemical processing operations, and degreasing operations can result in exposures that are much higher than those found in the outside environment. Levels of tetrachloroethylene in the workplace are usually measured in parts of tetrachloroethylene per million parts of air (ppm), while common environmental levels are usually measured in parts per billion (ppb) or parts per trillion (ppt).

1.3 HOW DOES TETRACHLOROETHYLENE GET INTO MY BODY?

Because tetrachloroethylene evaporates quickly, the most common exposure to tetrachloroethylene comes from breathing air containing it. This is certainly true for individuals who work with the chemical, but it is probably also true for those who live in industrial and commercial areas where large amounts of the compound are used or disposed of. Tetrachloroethylene may also enter the body through drinking contaminated water or eating contaminated food. Because tetrachloroethylene does not pass through the skin to any significant extent, entry into the body by this path is of minimal concern, although skin irritation may result from repeated or prolonged contact with the undiluted liquid. Scientific reports indicate that tetrachloroethylene is present (and may in fact be concentrated) in the breast milk of mothers who have been exposed to the chemical.

1.4 HOW CAN TETRACHLOROETHYLENE AFFECT MY HEALTH?

In high concentrations in air, particularly in closed, poorly ventilated areas, single exposures to tetrachloroethylene can cause central nervous system (CNS) effects leading to dizziness, headache, sleepiness, confusion, nausea, difficulty in speaking and walking, and possibly unconsciousness and death. As might be expected, these symptoms occur almost entirely in work (or hobby) environments. The potential long-term health effects that might occur in humans from breathing lower levels of tetrachloroethylene than those that produce CNS effects or from ingesting very low levels of the chemical found in some water supplies have not been identified. The effects of exposing infants to tetrachloroethylene through breast milk are unknown.

Animal studies, conducted with amounts much higher than typical environmental levels, have shown that tetrachloroethylene can cause liver and kidney damage, liver and kidney cancers, and leukemia (cancer of the tissues that form the white blood cells). Developmental effects in fetuses have been observed but only at tetrachloroethylene exposure levels that also produce toxicity in the maternal animal.

Based on evidence from animal studies, tetrachloroethylene is thought to be capable of causing cancer in humans. It should be emphasized, however, that currently available information is not sufficient to determine whether tetrachloroethylene causes cancer in humans.

1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO TETRACHLOROETHYLENE?

One way of testing for tetrachloroethylene exposure is to measure the amount of the chemical in the breath. This procedure has been used to measure levels of the chemical in persons living in areas where the air has been contaminated with tetrachloroethylene or in individuals occupationally exposed to the chemical. This procedure is only useful, however, if the exposure is recent (within weeks or less) because tetrachloroethylene is rapidly eliminated from the body. It is also possible to detect tetrachloroethylene in the blood. In addition, samples of blood and urine can be used to identify breakdown products of the chemical in persons suspected of being exposed to tetrachloroethylene. Although these procedures are relatively simple to perform, most physicians do not have the proper equipment and must rely on special laboratories to collect and analyze the samples. It should be noted that exposure to other chemical agents can produce the same breakdown products in the urine and blood. Therefore, these methods cannot be regarded as specific for tetrachloroethylene.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

The graphs on the following pages show the relationship between exposure to tetrachloroethylene and known health effects. In the first set of graphs (Fig. 1.1) labeled "Health effects from breathing tetrachloroethylene," exposure is measured in parts of tetrachloroethylene per million parts of air (ppm). In all graphs, effects in animals are shown on the left side and effects in humans on the right side.

In the second set of graphs (Fig. 1.2), the same relationship is represented for the known "Health effects from ingesting products containing tetrachloroethylene." Exposures are measured in milligrams of tetrachloroethylene per kilogram of body weight per day (mg/kg/day).

The first column on the graphs, labeled "Short-term exposure," refers to known health effects in laboratory animals and humans from exposure to tetrachloroethylene for 14 days or less. The column labeled "Long-term exposure" refers to tetrachloroethylene exposures of more than 14 days. The levels marked on the graphs as "Minimal risk for effects other than cancer" show estimates of levels of exposure at which no adverse effects are expected to occur. Because these levels are based largely on animal studies, some uncertainty still exists.

1.6.1 Toxic Effects Other Than Cancer

Figure 1.1 shows that short-term exposures to air containing more than 100 ppm of tetrachloroethylene have produced harmful effects in both humans and animals, and more prolonged exposures to approximately 9 ppm caused harmful liver effects in mice. It should be pointed out that some of the highest environmental levels of tetrachloroethylene ever recorded (at waste disposal sites, for example) were still 150 times smaller than the concentrations shown to produce symptoms of toxicity in animals after repeated exposure.

Figure 1.2 shows that drinking (or eating) the equivalent of approximately 60 to 80 mg (less than a spoonful) of undiluted tetrachloroethylene per kg of body weight (1 kg = 2.2 pounds) has produced effects similar to drinking alcohol. Tetrachloroethylene was used in the past as a medicine to eliminate worms in humans, but safer and more effective drugs are now available. More prolonged exposures in animals have produced harm to the liver at doses of approximately 100 mg/kg/day. These levels of exposure are more than 1,000 times higher than would be expected even if humans ingested the most contaminated drinking water ever reported.

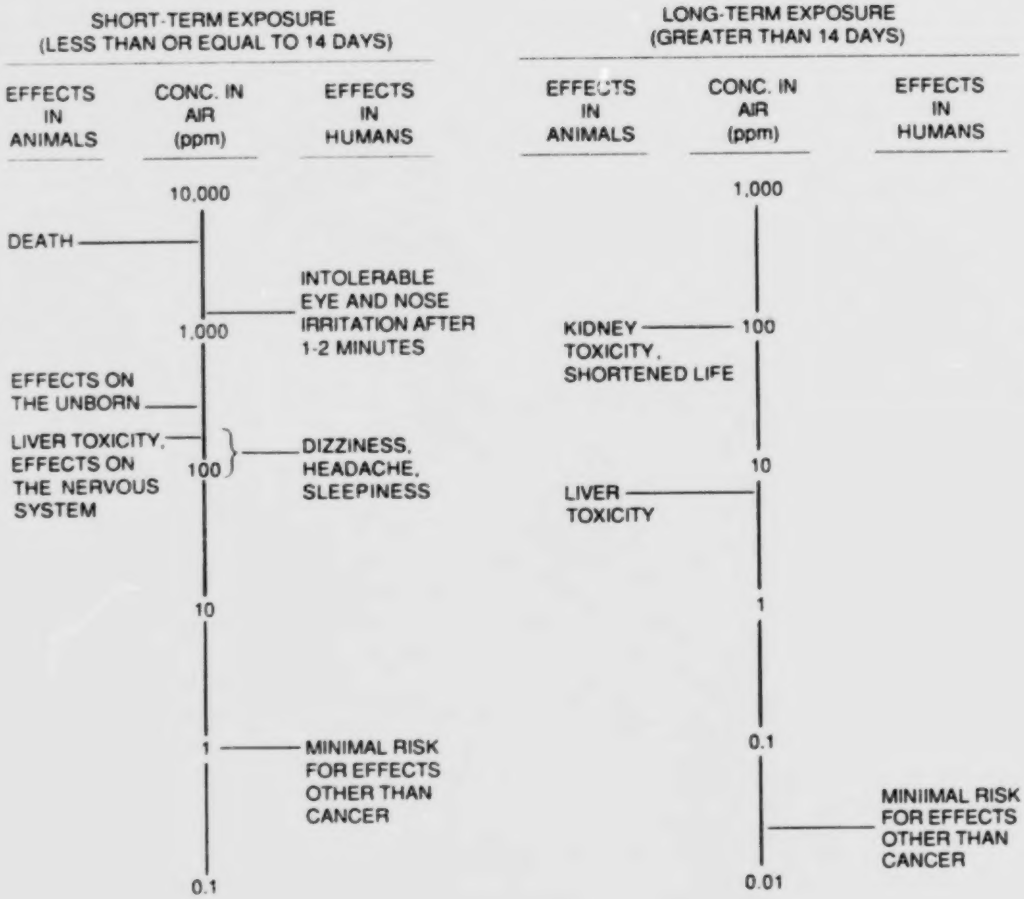

SHORT-TERM EXPOSURE
(LESS THAN OR EQUAL TO 14 DAYS)
EFFECTS IN ANIMALS
CONC. IN AIR (ppm)
EFFECTS IN HUMANS
10,000
DEATH
INTOLERABLE EYE AND NOSE IRRITATION AFTER 1-2 MINUTES
1,000
EFFECTS ON THE UNBORN
LIVER TOXICITY, EFFECTS ON THE NERVOUS SYSTEM
100
DIZZINESS, HEADACHE, SLEEPINESS
10
1
MINIMAL RISK FOR EFFECTS OTHER THAN CANCER
0.1
LONG-TERM EXPOSURE
(GREATER THAN 14 DAYS)
EFFECTS IN ANIMALS
CONC. IN AIR (ppm)
EFFECTS IN HUMANS
1,000
KIDNEY TOXICITY, SHORTENED LIFE
100
10
LIVER TOXICITY
1
0.1
MINIIMAL RISK FOR EFFECTS OTHER THAN CANCER
0.01

Fig. 1.1. Health effects from breathing tetrachloroethylene.

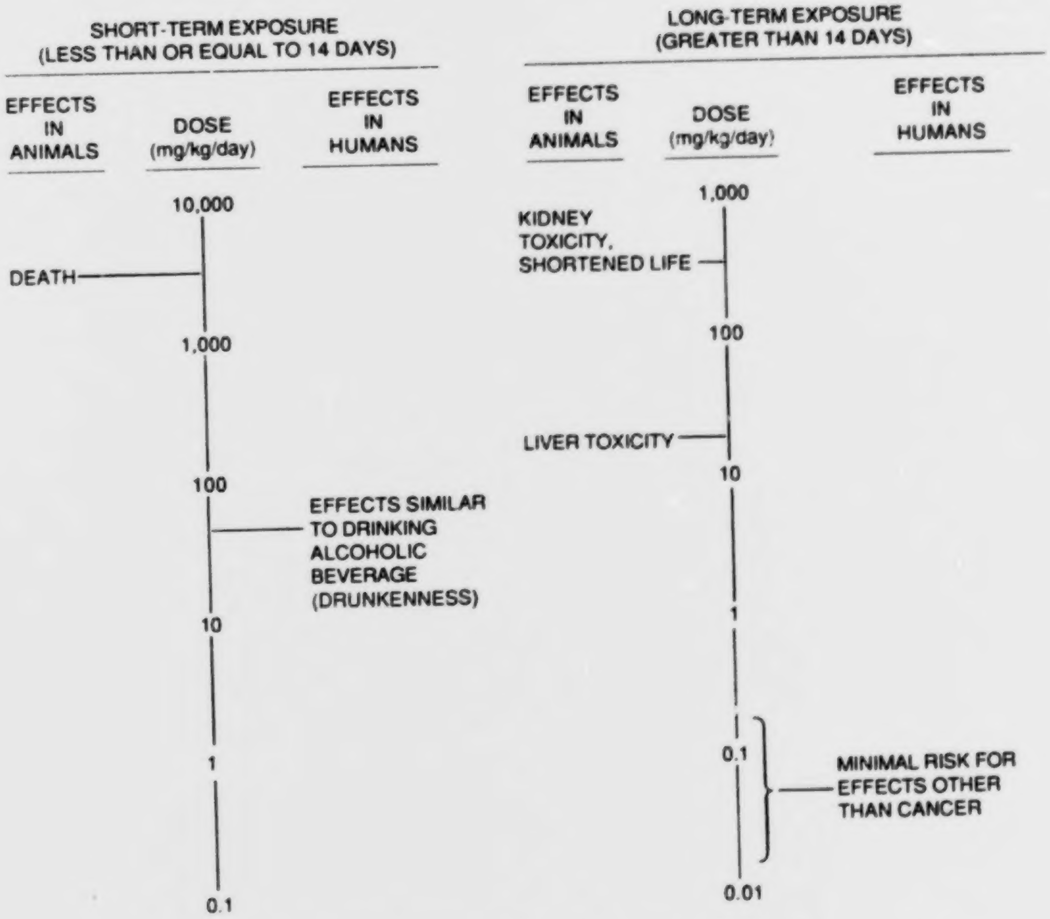


Fig. 1.2. Health effects from ingesting tetrachloroethylene.

1.6.2 Cancer

From data in animals, the EPA has estimated that if people breathe air containing 1 ppm tetrachloroethylene all day every day for 70 years, there would be an added risk of 66 additional cases of cancer in a population of 10,000 people (or 65,500 additional cases in a population of 10,000,000) over the number of cases that would be observed in a population not exposed to tetrachloroethylene. If people consume 1.0 mg tetrachloroethylene/kg/day in food and water every day for 70 years, there would be at the most a risk of 510 additional cases of cancer in a population of 10,000, or 510,000 additional cases in a population of 10,000,000. It should be noted that these risk values are plausible upper-limit estimates. Actual risk levels are unlikely to be higher and may be lower.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The government has made recommendations to limit the exposure of the general public to tetrachloroethylene in drinking water and the exposure of workers to tetrachloroethylene in the workplace.

The Environmental Protection Agency (EPA) has developed the following health advisories to describe concentrations of tetrachloroethylene in drinking water at which no adverse effects are anticipated to occur: 2.0 milligrams per liter of water (mg/L) for short-term exposure of children, 1.4 mg/L for longer term exposure of children, and 5.0 mg/L for long-term exposure of adults. In addition, a drinking water equivalent level (DWEL) of 0.5 mg/L has been established.

The Occupational Safety and Health Administration (OSHA) has a legally enforcible exposure limit of 100 ppm tetrachloroethylene in air for an 8-hour workday, 40-hour workweek based on noncancer health considerations. The National Institute for Occupational Safety and Health (NIOSH) has classified tetrachloroethylene as a potential occupational carcinogen and recommends that workplace exposure be limited to the lowest possible level.

2. HEALTH EFFECTS SUMMARY

2.1 INTRODUCTION

This section summarizes and graphs data on the health effects concerning exposure to tetrachloroethylene. The purpose of this section is to present levels of significant exposure for tetrachloroethylene based on key toxicological studies, epidemiological investigations, and environmental exposure data. The information presented in this section is critically evaluated and discussed in Sect. 4, Toxicological Data, and Sect. 7, Potential for Human Exposure.

This Health Effects Summary section comprises two major parts. Levels of Significant Exposure (Sect. 2.2) presents brief narratives and graphics for key studies in a manner that provides public health officials, physicians, and other interested individuals and groups with (1) an overall perspective of the toxicology of tetrachloroethylene and (2) a summarized depiction of significant exposure levels associated with various adverse health effects. This section also includes information on the levels of tetrachloroethylene that have been monitored in human fluids and tissues and information about levels of tetrachloroethylene found in environmental media and their association with human exposures.

The significance of the exposure levels shown on the graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of overt clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with frank effects (Frank Effect Level, FEL). Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (Lowest-Observed-Adverse-Effect Level, LOAEL) or exposure levels below which no adverse effects (No-Observed-Adverse-Effect Level, NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

Adequacy of Database (Sect. 2.3) highlights the availability of key studies on exposure to tetrachloroethylene in the scientific literature and displays these data in three-dimensional graphs consistent with the format in Sect. 2.2. The purpose of this section is to suggest where there might be insufficient information to establish levels of significant human exposure. These areas will be considered by the Agency for Toxic Substances and Disease Registry (ATSDR), EPA, and the National Toxicology Program (NTP) of the U.S. Public Health Service in order to develop a research agenda for tetrachloroethylene.

2.2 LEVELS OF SIGNIFICANT EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the toxicology data summarized in this section are organized first by route of exposure--inhalation, ingestion, and dermal--and then by toxicological end points that are categorized into six general areas--lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, genetic toxicity, and carcinogenicity. The data are discussed in terms of three exposure periods--acute, intermediate, and chronic.

Two kinds of graphs are used to depict the data. The first type is a "thermometer" graph. It provides a graphical summary of the human and animal toxicological end points (and levels of exposure) for each exposure route for which data are available. The ordering of effects does not reflect the exposure duration or species of animal tested. The second kind of graph shows Levels of Significant Exposure (LSE) for each route and exposure duration. The points on the graph showing NOAELs and LOAELs reflect the actual doses (levels of exposure) used in the key studies. No adjustments for exposure duration or intermittent exposure protocol re made.

Adjustments reflecting the uncertainty of extrapolating animal data to man, intraspecies variations, and differences between experimental vs actual human exposure conditions were considered when estimates of levels posing minimal risk to human health were made for noncancer end points. These MRLs were derived for the most sensitive noncancer end point for each exposure duration by applying uncertainty factors. These levels are shown on the graphs as a broken line starting from the actual dose (level of exposure) and ending with a concave-curved line at its terminus. Although methods have been established to derive these MRLs (Barnes et al. 1987), shortcomings exist in the techniques that reduce the confidence in the projected estimates. Also shown on the graphs under the cancer end point are low-level risks (10^{-4} - 10^{-7}) reported by EPA. In addition, the actual dose (level of exposure) associated with tumor incidence is plotted.

2.2.1 Key Studies and Graphical Presentations

Dose response-duration data for the toxicity and carcinogenicity of tetrachloroethylene are displayed in two types of graphs. These data are derived from the key studies described in the following sections. The "thermometer" graphs in Figs. 2.1 and 2.2 plot exposure levels vs NOAELs and LOAELs for various effects and durations of inhalation and oral exposures, respectively. The graphs of levels of significant exposure in Figs. 2.3 and 2.4 plot end-point-specific NOAELs and LOAELs, and MRLs for acute (≤14 days), intermediate (15-364 days), and chronic (≥365 days) durations for inhalation and oral exposures, respectively.

2.2.1.1 Inhalation

Lethality and decreased longevity. Data regarding inhalation exposure levels that produce death in humans were not available. An inhalation LC_{50} of 5,200 ppm for 4 h for mice was reported by Friberg et al. (1953). Other data indicate that single 4-h exposures to 2,445 and

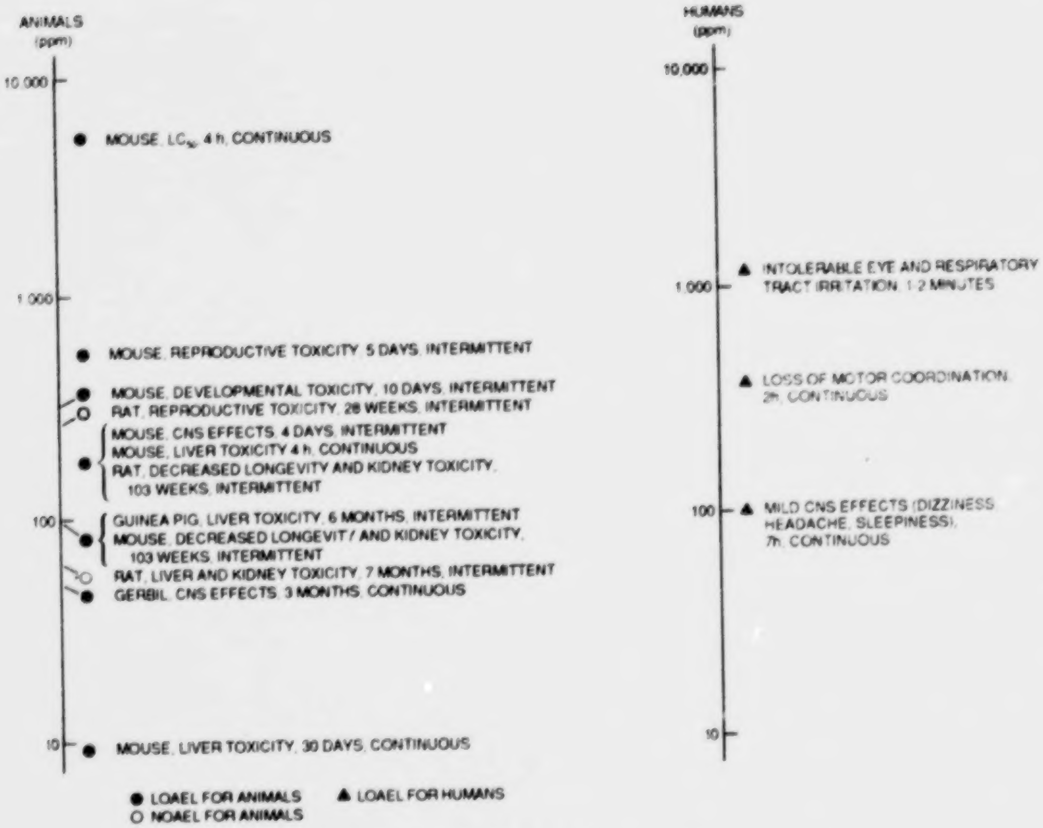


Fig. 2.1. Effects of tetrachloroethylene—inhalation exposure.

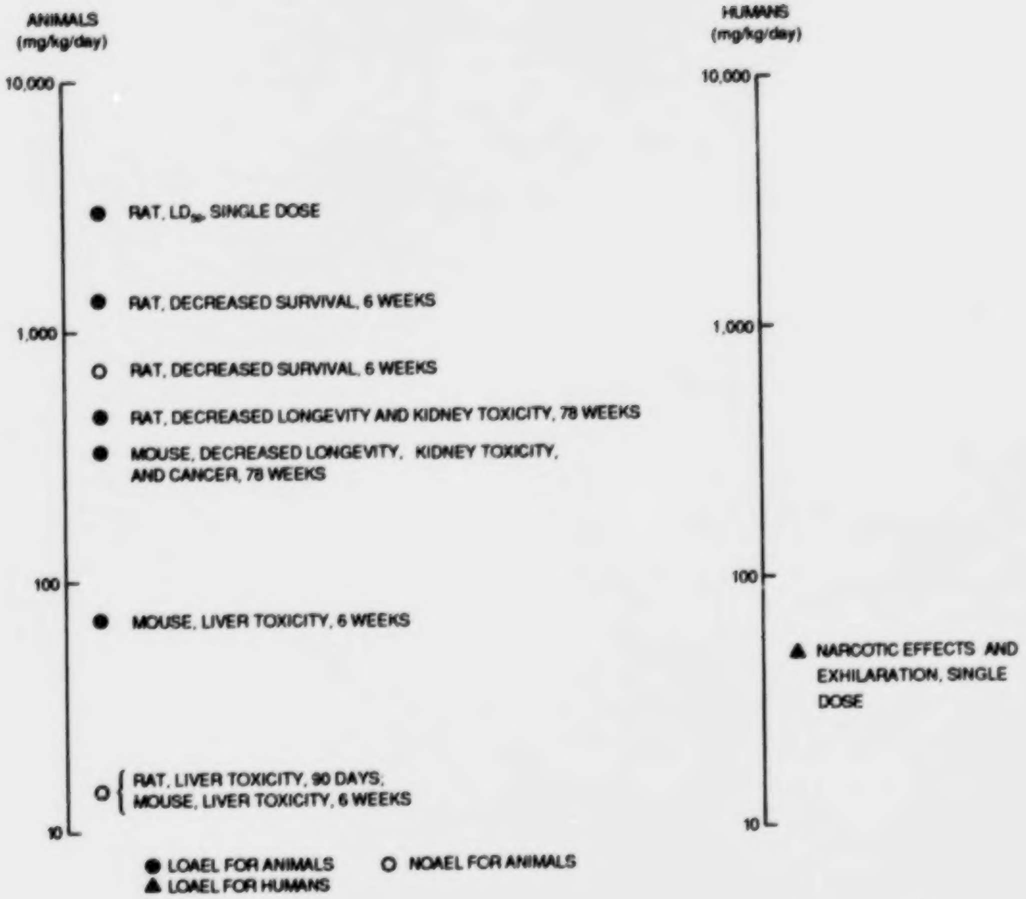


Fig. 2.2. Effects of tetrachloroethylene—oral exposure.

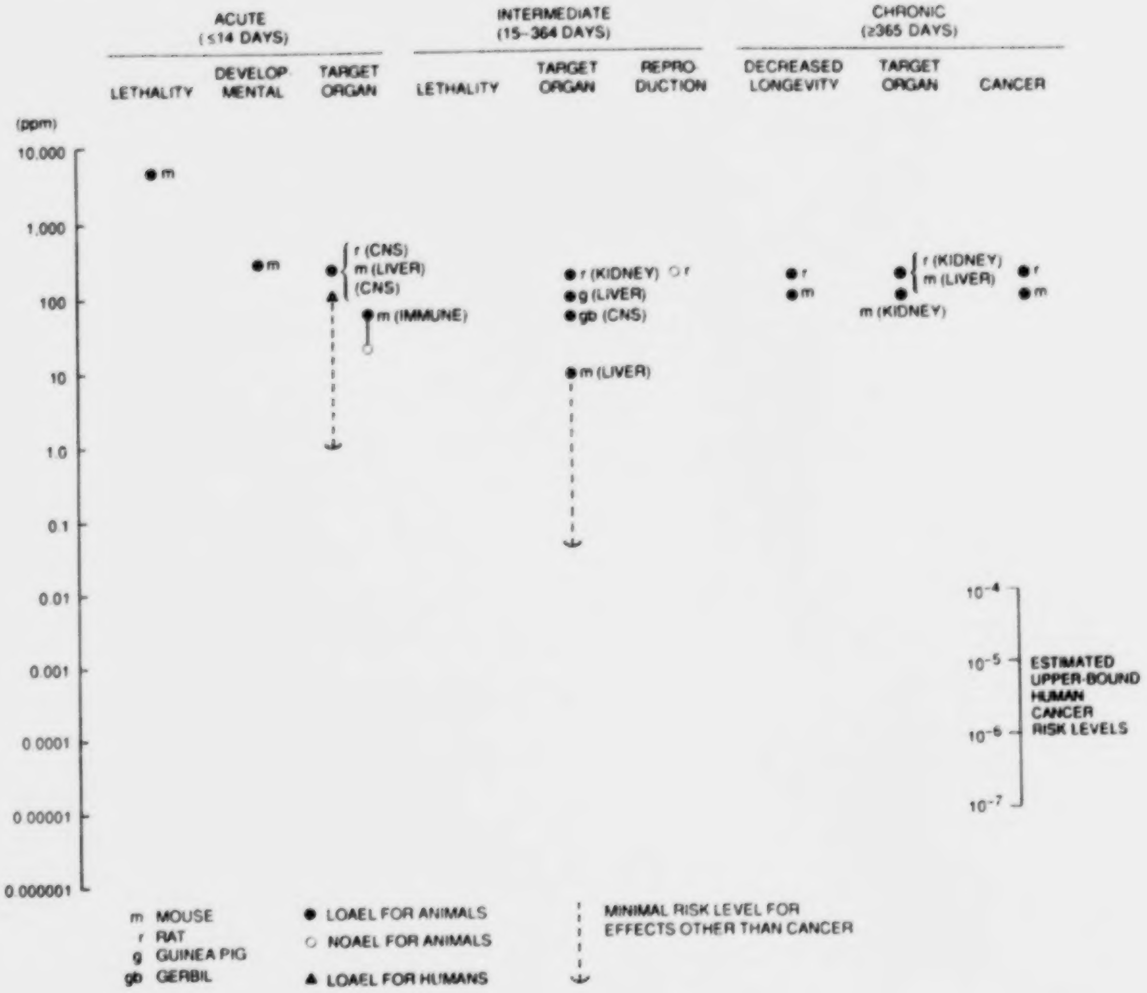


Fig. 2.3. Levels of significant exposure for tetrachloroethylene—inhalation.

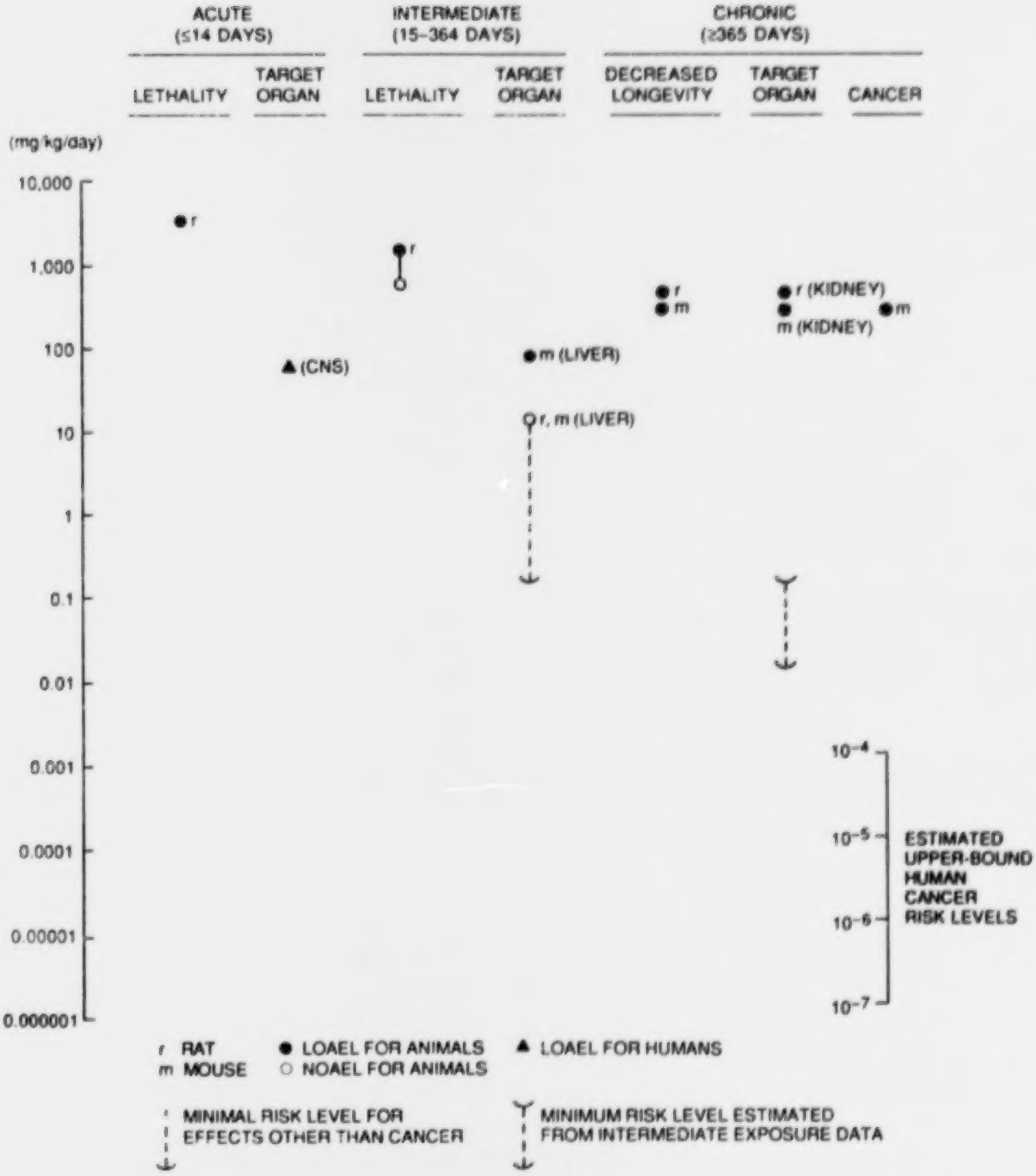


Fig. 2.4. Levels of significant exposure for tetrachloroethylene—oral.

2,450 ppm were not lethal to rats or mice (NTP 1986) or to mice alone, respectively (Friberg et al. 1953). Rowe et al. (1952) reported that single 10- or 14-h exposures to 2,000 ppm and a single 4-h exposure to 3,000 ppm did not produce mortality in rats, and that exposure to 3,000 ppm for 5 h or longer produced some mortality (2/15, 3/10, and 2/5 dead rats/number exposed at exposure durations of 5, 6, and 8 h, respectively). The LC_{50} is displayed as a LOAEL for acute lethality in Figs. 2.1 and 2.3. A NOAEL for acute lethality is not included in Figs. 2.1 and 2.3 because the effects of acute exposure duration on lethality are uncertain.

Rats and mice were exposed to tetrachloroethylene by inhalation for 6 h/day, 5 days/week for 14 days or 13 weeks in other preliminary NTP (1986) studies. Survival data from both of these studies are consistent, showing that treatment-related mortality occurred only at the highest exposure concentration (1,750 ppm in the 14-day study and 1,600 ppm in the 13-week study). The ratio of deceased rats/exposed rats was 5/10 at the 1,750-ppm exposure level in the 14-day study and 6/20 at the 1,600-ppm exposure level in the 13-week study. Survival was not affected in either rats or mice by exposure to ≤875 ppm in the 14-day study or to ≤800 ppm in the 13-week study. A recent abstract indicates, however, that rats exposed continuously to 800 ppm tetrachloroethylene for 12 weeks experienced 70% mortality (Nomiyama et al. 1986).

Rats were exposed to 0, 200, or 400 ppm and mice to 0, 100, or 200 ppm tetrachloroethylene for 6 h/day, 5 days/week for 103 weeks in an NTP (1986) carcinogenicity bioassay. Reduced survival occurred at all concentrations in both species. The lowest concentration, 100 ppm, which caused decreased survival in male but not female mice, is indicated as a LOAEL for decreased longevity in mice in Figs. 2.1 and 2.3. The value of 200 ppm, which caused decreased survival in rats, is presented as a LOAEL for decreased longevity in Figs. 2.1 and 2.3.

Systemic/target organ toxicity. The CNS, liver, and kidney are the main target organs of inhalation exposure to tetrachloroethylene. In humans, quantitative exposure effect data are available only for CNS effects resulting from acute exposure (Hake and Stewart 1977; Rowe et al. 1952; Stewart et al. 1970, 1977). These data are limited by the small number of subjects, predominantly subjective effects, differences in exposure duration, the small number of studies, and discrepancies between the studies. For these reasons, none of the studies provide adequate exposure-effect data when considered individually. When considered collectively, however, they indicate that the threshold for effects such as dizziness, headache, sleepiness, and incoordination occurs in the range of 100 to 200 ppm for 5.5- to 7-h exposures. Unquantified reports of accidental exposures indicate that acute exposures to higher concentrations of tetrachloroethylene produce CNS effects that are more severe than those described above, including loss of coordination, nausea, and unconsciousness. Limited acute inhalation data are available for animals: exposure to 200 ppm for 4 h produced reversible fatty degeneration of the liver in mice (Kylin et al. 1963); exposure to 200 ppm for 6 h/day for 4 days produced reversible, increased open-field activity, reduced brain RNA content, and increased brain nonspecific cholinesterase content in rats (Savolainen et al. 1977); and exposure to >1,000 ppm for 4 to 7 h/day for several days produced loss of coordination and anesthesia in rats (Carpenter 1937, Rowe et al. 1952, Goldberg et al. 1964). As these effects occurred at higher concentrations than the apparent threshold for CNS effects in humans (100 to 200 ppm), it is appropriate to regard 100 ppm as the LOAEL for target organ toxicity for acute inhalation exposures (see Fig. 2.1). Since a NOAEL is not available, the 100-ppm LOAEL is the basis for the MRL (Fig. 2.3).

There is some indication that exposure to tetrachloroethylene may diminish pulmonary bactericidal activity. Mice exposed to 50 but not 25 ppm tetrachloroethylene for 3 h showed increased susceptibility to a streptococcal aerosol challenge (Aranyi et al. 1986). Complications in interpreting these data (see Sect. 4.3.2.4 on Immunotoxicity in Toxicological Data) preclude their use in risk assessment, and the human LOAEL of 100 ppm remains the most appropriate basis for deriving an MRL.

Case reports indicate that extended (beyond short-term) inhalation exposure to tetrachloroethylene increases the severity and duration of many of the CNS symptoms resulting from short-term exposure and produces other CNS effects (e.g., ataxia, irritability, short-term memory deficits); however, quantitative data are not available (EPA 1985a). In intermediate duration inhalation studies with animals, exposure to 9 ppm continuously for 30 days produced liver enlargement and vacuolization of hepatocytes in mice (Kjellstrand et al. 1984); exposure to 37 ppm and higher concentrations induced more pronounced hepatic pathological alterations. Continuous exposure to 60 ppm for 3 months followed by 4 months without exposure caused decreased DNA content in the frontal cerebral cortex of gerbils (Rosengren et al. 1986), and continuous exposure to 120 ppm for 12 months caused other biochemical alterations in the brains of gerbils (Briving et al. 1986, Kyrklund et al. 1984). Carpenter (1937) did not find pathological alterations in the livers or kidneys of rats exposed to 70 ppm for 8 h/day, 5 days/week for 7 months, but histological effects were evident in the kidneys at ≥230 ppm. Increased liver weights occurred in guinea pigs exposed to 100 ppm for 7 h/day, 5 days/week for ~6 months (Rowe et al. 1952), but there were hepatic histological alterations at ≥200 ppm in this study and in intermittent-exposure, intermediate-duration studies with mice and rats (Kylin et al. 1965, NTP 1986). In the Rowe et al. (1952) study, no histopathological changes were observed in rats, rabbits, or monkeys exposed to up to 400 ppm 7 h/day, 5 days/week for ~6 months.

The results of intermediate-duration studies with animals, therefore, indicate that adverse effects in the liver are associated with continuous exposure to ≥9 ppm in mice (Kjellstrand et al. 1984) and intermittent exposure to ≥100 ppm in guinea pigs, mice, and rats (Carpenter 1937, Rowe et al. 1952, Kylin et al. 1965, NTP 1986). Continuous exposure to ≥60 ppm caused biochemical alterations in the brain of gerbils (Rosengren et al. 1986, Briving et al. 1986, Kyrklund et al. 1984). Since 9 ppm is the lowest concentration tested in intermediate-duration inhalation studies, it is the LOAEL for target organ effects of intermediate exposure (Fig. 2.1) and the basis for the MRL (see Fig. 2.3). The results of Kjellstrand et al. (1984) and the continuous-exposure study by Rosengren et al. (1986) indicate that tetrachloroethylene is more toxic when administered continuously for shorter durations than intermittently for longer durations.

In the only chronic inhalation study, exposure to 100 or 200 ppm for 6 h/day, 5 days/week for 103 weeks produced renal tubular-cell karyomegaly in mice and rats (NTP 1986); exposure to 200 ppm also produced nonneoplastic hepatic lesions (including degeneration and necrosis) in mice. Although 100 ppm represents a LOAEL for target organ effects, reduced survival (a FEL) at 100 ppm indicates that these target organ effects are not the most sensitive end point for chronic exposure; therefore, they present an inappropriate basis for an MRL.

Epidemiology data (Hara et al. 1985) and a single case report (Abedin et al. 1980) associate inhalation exposure to tetrachloroethylene with cardiotoxic effects, possibly sensitization of the myocardium to epinephrine-induced arrhythmias (Abedin et al. 1980). Human data were insufficient for deriving thresholds, but inhalation data in dogs suggest that myocardial sensitization does not occur in this species at 10,000 ppm (Reinhardt et al. 1973). Myocardial sensitization to the epinephrine challenge has been shown in rabbits, cats, and dogs given high intravenous doses of tetrachloroethylene (Kabayashi et al. 1982).

Developmental toxicity. Data regarding human developmental effects of inhaled tetrachloroethylene were not available. In a developmental toxicity study with mice and rats, mice exposed to 300 ppm for 7 h/day on days 6 to 15 of gestation had increased maternal liver weights and embryotoxic effects (decreased fetal weight, increased incidences of subcutaneous edema, delayed ossification of the skull, and split sternebrae), but no terata (Schwetz et al. 1975). In rats, effects observed were limited to an increased percentage of fetal resorptions and decreased maternal body weight. Similar effects (maternal toxicity and fetotoxicity, including skeletal ossification anomalies) were observed in rats exposed to a nominal concentration of 300 ppm tetrachloroethylene during gestation (Beliles et al. 1980); however, there was evidence that the targeted exposure concentrations had been significantly exceeded. In other developmental toxicity studies with rats, gestational exposure to 1,000 (Tepe et al. 1982, Manson et al. 1982) but not 900 ppm (Nelson et al. 1980) tetrachloroethylene produced embryotoxic effects, including skeletal anomalies. The emphasis of the Nelson et al. (1980) study, however, was on behavioral effects; traditional parameters of fetotoxicity were inadequately reported. In a behavioral teratology study, rats were exposed 7 h/day to 0, 100, or 900 ppm on days 7 to 13 or 14 to 20 of gestation (Nelson et al. 1980). Inconsistently decreased performance on tests of neuromuscular ability, increased open-field activity, and decreased content of brain dopamine and acetylcholine occurred in the offspring of the 900- but not the 100-ppm exposed rats. Because 100 ppm is an equivocal NOAEL for developmental effects (traditional parameters of fetotoxicity were not evaluated at this concentration), only the lowest FEL (300 ppm) is included in Figs. 2.1 and 2.3. The overall evidence indicates that tetrachloroethylene is not teratogenic in animals and any fetotoxic effects are apparent only at exposure levels that are maternally toxic.

Reproductive toxicity. An increased frequency of abnormal sperm was observed in mice exposed to 500 but not 100 ppm for 7 h/day on 5 consecutive days (Beliles et al. 1980). There were no adverse effects on reproductive performance in rats exposed to 70, 230, or 470 ppm for

8 h/day, 5 days/week for 28 weeks (Carpenter 1937). Since 470 and 500 ppm represent the highest NOAEL and LOAEL, respectively, they are included in Figs. 2.1 and 2.3. Also, since target organ effects occurred at similar and lower concentrations than this NOAEL, an MRL for reproductive effects is not calculated.

Genotoxicity. Chromosome aberrations and sister chromatid exchange were not detected in lymphocytes from workers who were occupationally exposed to tetrachloroethylene (Ikeda et al. 1980). Equivocal results were obtained in an unscheduled DNA synthesis assay with human fibroblasts (Beliles et al. 1980). Predominantly negative responses occurred in various in vivo and in vitro assays of microbial and animal systems. The NTP (1986) reported that tetrachloroethylene was not mutagenic in *Salmonella typhimurium* (strains TA98, TA100, TA1535, or TA1537) or in L5178Y/TK +/- mouse lymphoma cells with or without metabolic activation. Tetrachloroethylene did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* and did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells either with or without metabolic activation (NTP 1986). Some positive responses were reported when technical and commercial-grade tetrachloroethylene samples were evaluated in in vitro test systems. However, these responses were only observed at high concentrations and were not dose-dependent. The EPA (1985a) suggested that these positive genotoxic findings could have been the results of contaminants and/or stabilizers of the tetrachloroethylene products tested (see Sect. 4.3.5).

Carcinogenicity. NTP (1986) found significantly increased incidences of mononuclear cell leukemia in both male and female rats exposed to 200 or 400 ppm tetrachloroethylene. Both male and female mice exposed to 100 or 200 ppm tetrachloroethylene according to the same schedule showed significantly increased incidences of hepatocellular carcinomas at both concentrations (NTP 1986). The EPA (1986) used the results of the NTP (1986) bioassay as the basis for a quantitative carcinogenicity risk assessment for inhalation exposure to tetrachloroethylene. Six sets of incidence data were used: mononuclear cell leukemia in male and female rats, liver carcinomas in male and female mice, and combined incidences of liver adenomas and carcinomas in male and female mice. Based on potency estimates calculated from the six sets of tumor incidence data, EPA (1986) calculated an incremental risk range of $2.85\text{-}9.47 \times 10^{-7}$ for humans exposed to tetrachloroethylene at a concentration of 1 $\mu g/m^3$ in air. Using the most conservative upper-bound estimate of risk, 9.47×10^{-7} $(\mu g/m^3)^{-1}$, the exposure levels associated with increased lifetime upper-bound cancer risks of 1×10^{-4} to 1×10^{-7} are 1.6×10^{-2} to 1.6×10^{-5} ppm. These exposure levels are indicated in Fig. 2.3.

2.2.1.2 Oral

Lethality and decreased longevity. Tetrachloroethylene has been administered orally to humans at doses of 2.8 to 4.0 mL (~4.2 to 6 g, or 60 to 86 mg/kg, assuming a 70-kg body weight) as an antihelminthic (Lambert 1933). Since these were therapeutic doses, 60 mg/kg represents a NOAEL for acute lethality. The NOAEL is not used to calculate an MRL, however, because a single case report suggests that ingestion of a similar dose (3 mL) may have been lethal (Chaudhuri and Mukerji 1947). Oral, single-dose 14-day LD50s of 3,835 and 3,005 mg/kg were determined for male and female rats (Hayes et al. 1986). The lower LD50 is included in Figs. 2.2 and 2.4 as a LOAEL for acute lethality.

Deaths occurred in rats treated with >1,780 but not ≤1,000 mg/kg by gavage 5 days/week for 6 weeks (NCI 1977). When adjusted for partial weekly exposure, the highest NOAEL is 714 mg/kg/day and the lowest LOAEL is 1,271 ppm. These doses are plotted for intermediate lethality in Figs. 2.2 and 2.4.

Rats and mice exposed by gavage to time-weighted-average (TWA) doses of ≥471 and ≥300 mg/kg/day, respectively, for 78 weeks, followed by 32 and 12 weeks, respectively, of observation experienced reduced survival (NCI 1977). The lowest TWA dose, 300 mg/kg/day, is included in Figs. 2.2 and 2.4 as a LOAEL for decreased longevity for chronic exposure.

Systemic/target organ toxicity. The main target organs of oral exposure to tetrachloroethylene appear to be the CNS, liver, and kidneys, although human evidence is limited, and animal data for CNS effects are not available. For acute exposures, ingestion of 2.8- to 4-mL (~4.2 to 6 g, or 60 to 86 mg/kg, assuming a 70-kg body weight) doses as an antihelminthic reportedly caused narcotic effects and exhilaration (without death) in humans (Lambert 1933). Symptoms and/or signs of liver and kidney dysfunction were associated with accidental ingestion of tetrachloroethylene in humans, but quantitative data were not available (Koppel et al. 1985, EPA 1985a). A dose of 60 mg/kg/day in humans is plotted as a LOAEL for CNS effects in Figs. 2.2 and 2.4. Although this LOAEL appears to be based on human therapeutic experience, it is not used to calculate an MRL for acute exposure, because a case report suggests that ingestion of a similar dose (3 mL) may have been lethal (Chaudhuri and Mukerji 1947).

Intermediate- and chronic-duration toxicity data for oral exposure are not available for humans. In mice, gavage exposure to ≥100 but not 20 mg/kg 5 days/week for 6 weeks produced dose-related hepatic alterations (Buben and O'Flaherty 1985). Effects included increased liver weight and triglycerides at ≥100 mg/kg and degenerative changes and related histological alterations at ≥200 ppm. Male rats exposed to 400 or 1,400 mg/kg/day and females exposed to 1,400 mg/kg/day via drinking water for 90 days had increased levels of serum 5'nucleotidase (an indicator of possible liver damage). Male rats showed increased relative (organ-to-body weight) kidney weights at ≥400 mg/kg/day and increased relative liver weights at 1,400 mg/kg/day. Female rats showed increased relative kidney and liver weights only at the 1,400-mg/kg/day dosage. Body weights (terminal) were depressed in males at the highest dose and in females at both 400 and 1,400 mg/kg/day. No effects were noted in either sex at 14 mg/kg/day (Hayes et al. 1986). Limitations in these studies include histological examination of only the liver in the Buben and O'Flaherty (1985) study and no histological examinations in the Hayes et al. (1986) study. These limitations are mitigated by the similarity of the NOAELs (20 mg/kg 5 days/week and 14 mg/kg/day 7 days/week), particularly when the 20-mg/kg dose is adjusted for partial weekly exposure (14.3 mg/kg/day). The 14-mg/kg/day dose from both studies (Buben and O'Flaherty 1985, Hayes et al. 1986) is chosen as the basis for deriving an MRL for intermediate oral exposure. The NOAEL, the MRL, and the lowest LOAEL [100 mg/kg (71.4 mg/kg/day when adjusted for partial weekly exposure)] are plotted in Figs. 2.2 and 2.4.

In the only chronic oral study (NCI 1977), rats and mice were exposed to TWA doses of ≥471 or ≥300 mg/kg/day, respectively, by gavage 5 days/week for 78 weeks, followed by observation periods of 32 weeks (rats) or 12 weeks (mice). Toxic nephropathy occurred in all treatment groups in both species; the lowest TWA dose was 300 mg/kg/day in male mice. This LOAEL is included in Figs. 2.2 and 2.4, but it is not used to calculate an MRL for chronic oral exposure because increased mortality also occurred at this dose. The 14-mg/kg/day NOAEL for intermediate-duration oral exposure (Hayes et al. 1986) serves as the basis for the MRL for chronic oral exposure, as derived by the EPA (1987) (see Fig. 2.4).

Developmental toxicity. Pertinent data regarding developmental toxicity due to oral exposure to tetrachloroethylene were not found in the available literature.

Reproductive toxicity. Pertinent data regarding reproductive effects of oral exposure to tetrachloroethylene were not found in the available literature.

Genotoxicity. See Sect. 2.2.1.1 in this profile.

Carcinogenicity. NCI (1977) found significantly increased incidences of hepatocellular carcinomas in male and female mice treated with tetrachloroethylene by gavage 5 days/week for 78 weeks, followed by an observation period of 12 weeks. TWA doses for the mice were 450 and 550 mg/kg/day for males and 300 and 400 mg/kg/day for females. Rats were also evaluated in this study, but the rat data were considered inconclusive because of excess mortality. The EPA (1985a) calculated potency estimates for tetrachloroethylene based on the incidence of hepatocellular carcinoma in female mice from the NCI (1977) study. Because tetrachloroethylene metabolism was nonlinear in the experimental dose range of the NCI mouse study, animal potency estimates were based on metabolized dose determined from the urinary excretion of tetrachloroethylene metabolites. Two different data sets were used, which yielded comparable results. The urinary metabolite curve was generated from the data of Buben and O'Flaherty (1985). Animal metabolized dose was converted to estimated human metabolized dose using a surface area approximation. To convert animal metabolized dose to a theoretical human administered dose, it was assumed that 20% of the administered dose would be metabolized. The EPA (1985a) chose the potency estimate based on the tumor response in female mice to characterize the potency of tetrachloroethylene because of the clearer dose-response relationship in tumor incidence levels for this sex.

The overall weight of the evidence for the carcinogenicity of tetrachloroethylene is currently under review. EPA (1986) has recommended a Group B2 weight-of-evidence classification. EPA's Science Advisory Board has commented that a continuum between Group C and B2 may be appropriate. IARC (1987) has considered the data and given a classification of 2B. As of January 1989, EPA has not taken a final position on the weight of evidence. Using the q_1* of 5.1 × 10^{-2} $(mg/kg/day)^{-1}$, the oral doses associated with individual lifetime upper-bound cancer risks of 1 × 10^{-4} to 1 × 10^{-7} are 2.0 × 10^{-3} to 2.0 × 10^{-6} mg/kg/day. These doses are indicated in Fig. 2.4.

2.2.1.3 Dermal

Lethality and decreased longevity. Pertinent data regarding lethality and reduced longevity because of dermal exposure to tetrachloroethylene were not found in the available literature.

Systemic/target organ toxicity. Pertinent data regarding systemic or target organ toxicity because of dermal exposure to tetrachloroethylene were not found in the available literature.

Developmental toxicity. Pertinent data regarding developmental toxicity because of dermal exposure to tetrachloroethylene were not found in the available literature.

Reproductive toxicity. Pertinent data regarding the reproductive effects of dermal exposure to tetrachloroethylene were not found in the available literature.

Genotoxicity. See Sect. 2.2.1.1 in this profile.

Carcinogenicity. Tetrachloroethylene did not produce papillomas or carcinomas of the skin or tumors at any distant sites following dermal application of the compound to female Ha:IRC mice over the course of a lifetime (Van Duuren et al. 1979).

2.2.2 Biological Monitoring as a Measure of Exposure and Effects

2.2.2.1 Exposure

Biological monitoring for exposure to tetrachloroethylene is possible by measuring levels of either the parent compound or the metabolites in the blood, urine, or exhaled air. Biological monitoring for tetrachloroethylene exposure has been performed to measure both exposure occurring in the workplace and the environmental exposure of individuals at places other than the work site. In these instances, it has been demonstrated by several studies that measurement of the parent compound (tetrachloroethylene) in exhaled air is a fairly simple, effective, and noninvasive method for assessing both occupational and nonoccupational exposure. Measurement of tetrachloroethylene in the exhaled air has also been found to be superior to measurement of metabolic products, which are not specific. Sources of tetrachloroethylene in nonoccupationally exposed individuals are indicated in Sect. 1.2. The concentration of tetrachloroethylene in exhaled air was used to measure environmental exposure to the compound in a group of 54 healthy volunteers from an urban population (Krotoszynski et al. 1979). In this group of subjects, it was determined that 30.2% had traces of tetrachloroethylene in their breath, with a mean concentration of 2.6 $\mu g/m^3$. The measurement of tetrachloroethylene in exhaled air was used to determine that 93% of a sample of ~300 nonoccupationally exposed residents of Bayonne and Elizabeth, New Jersey, had measurable concentrations of tetrachloroethylene in their breath (Wallace 1986). The mean concentration of tetrachloroethylene in the breath in this study was 13.3 μg/m^3, and this mean concentration was increased to 22 μg/m^3 for persons who had visited a dry-cleaning establishment. Monster and Smolders (1984) used measurements of tetrachloroethylene in exhaled air to determine exposure in children attending a school near a factory and in occupants of a senior citizens home located near a former chemical waste dump. "Control" children had mean tetrachloroethylene levels in their exhaled air of 2.8 μg/m^3, whereas "exposed" children had mean tetrachloroethylene levels of 24 μg/m^3. In the senior citizen group, people living on the first floor of the home had tetrachloroethylene levels of 7.8 μg/m^3, whereas people living on the second floor and above had tetrachloroethylene levels of 1.8 μg/m^3. Monster and Smolders (1984) concluded that biological monitoring of tetrachloroethylene in exhaled air was an effective method of assessing total ambient tetrachloroethylene exposure in both the young and aged.

Biological monitoring for exposure to tetrachloroethylene has also been performed by measuring concentrations of tetrachloroethylene and its principal metabolites [trichloroacetic acid (TCA) and trichloroethanol (TCE)] in blood and urine. Ramsey and Flanagan (1982) described a gas chromatographic method for measuring tetrachloroethylene in the blood (detection limit of 10 μg/L), and Ziglio et al. (1984) described a gas chromatographic method for detecting TCA (a terminal metabolite of tetrachloroethylene) in plasma (detection limit of 2 μg/L). Monster et al. (1983) described procedures for monitoring occupational exposure to tetrachloroethylene that involve measuring tetrachloroethylene in blood and exhaled air, TCA and TCE in urine, and TCA in blood. In this study, measurement of tetrachloroethylene and trichloroacetic acid in the blood 15-30 min after the end of the workday at the end of the week were judged to be the best parameters for estimating exposure to the chemical. The best noninvasive method for determining tetrachloroethylene exposure was to measure the concentration in exhaled air. After exposure to a time-weighted-average concentration of 50 ppm of tetrachloroethylene, the concentration of tetrachloroethylene and trichloroacetic acid in blood were 13.2 and 33 μmol/L, respectively; the concentration of tetrachloroethylene in exhaled air was 920 μmol/m^3.

2.2.2.2 Effects

Methods of biological monitoring for measuring the effects of exposure to tetrachloroethylene were not found in the available literature.

2.2.3 Environmental Levels as Indicators of Exposure and Effects

2.2.3.1 Levels found in the environment

A summary of tetrachloroethylene monitoring data for air, water, soil, and food is presented in Sect. 7. Data regarding the association between significant human exposure or effects and levels of tetrachloroethylene found in soil, water, and food were not found in the available literature. Several investigators have found a correlation between levels of tetrachloroethylene in the inhalable ambient air and levels in human breath, which indicates that elevated levels in human breath (expired air) are associated with elevated levels in ambient air (Wallace 1986; Wallace et al. 1986a,b; Monster and Smolders 1984; Krotoszynski et al. 1979).

2.2.3.2 Human exposure potential

Measurable levels above typical background concentrations have been shown to be emitted to the ambient air by means of evaporative losses from waste disposal sites (Sect. 7). Therefore, inhalation is expected to be the dominant route of human exposure at these waste sites. In addition to atmospheric losses, significant losses of tetrachloroethylene by leaching to groundwaters have also been shown to occur at waste disposal sites. A human exposure potential will therefore exist when the contaminated groundwaters are used by humans for potable and nonpotable water supplies. Tetrachloroethylene exposure to humans from contaminated water can occur through routes such as consumption (drinking water), dermal contact (showers, baths), and inhalation (tetrachloroethylene readily volatilizes from water).

2.3 ADEQUACY OF DATABASE

2.3.1 Introduction

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each of the 100 most significant hazardous substances found at facilities on the CERCLA National Priorities List. Each profile must include the following content:

"(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

This section identifies gaps in current knowledge relevant to developing levels of significant exposure for tetrachloroethylene. Such gaps are identified for certain health effect end points (lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, and carcinogenicity) reviewed in Sect. 2.2 of this profile in developing levels of significant exposure for tetrachloroethylene, and for other areas such as human biological monitoring and mechanisms of toxicity. The present section briefly summarizes the availability of existing human and animal data, identifies data gaps, and summarizes research in progress that may fill such gaps.

Specific research programs for obtaining data needed to develop levels of significant exposure for tetrachloroethylene will be developed by ATSDR, NTP, and EPA in the future.

2.3.2 Health Effect End Points

2.3.2.1 Introduction and graphic summary

The availability of data for health effects in humans and animals is depicted on bar graphs in Figs. 2.5 and 2.6, respectively.

The bars of full height indicate that there are data to meet at least one of the following criteria:

1. For noncancer health end points, one or more studies are available that meet current scientific standards and are sufficient to define a range of toxicity from levels that cause no effects (NOAELs) to levels that cause effects (LOAELs or FELs).

2. For human carcinogenicity, a substance is classified as either a "known human carcinogen" or "probable human carcinogen" by both EPA and the International Agency for Research on Cancer (IARC) (qualitative), and the data are sufficient to derive a cancer potency factor (quantitative).

3. For animal carcinogenicity, a substance causes a statistically significant number of tumors in at least one species, and the data are sufficient to derive a cancer potency factor.

4. There are studies which show that the chemical does not cause this health effect via this exposure route.

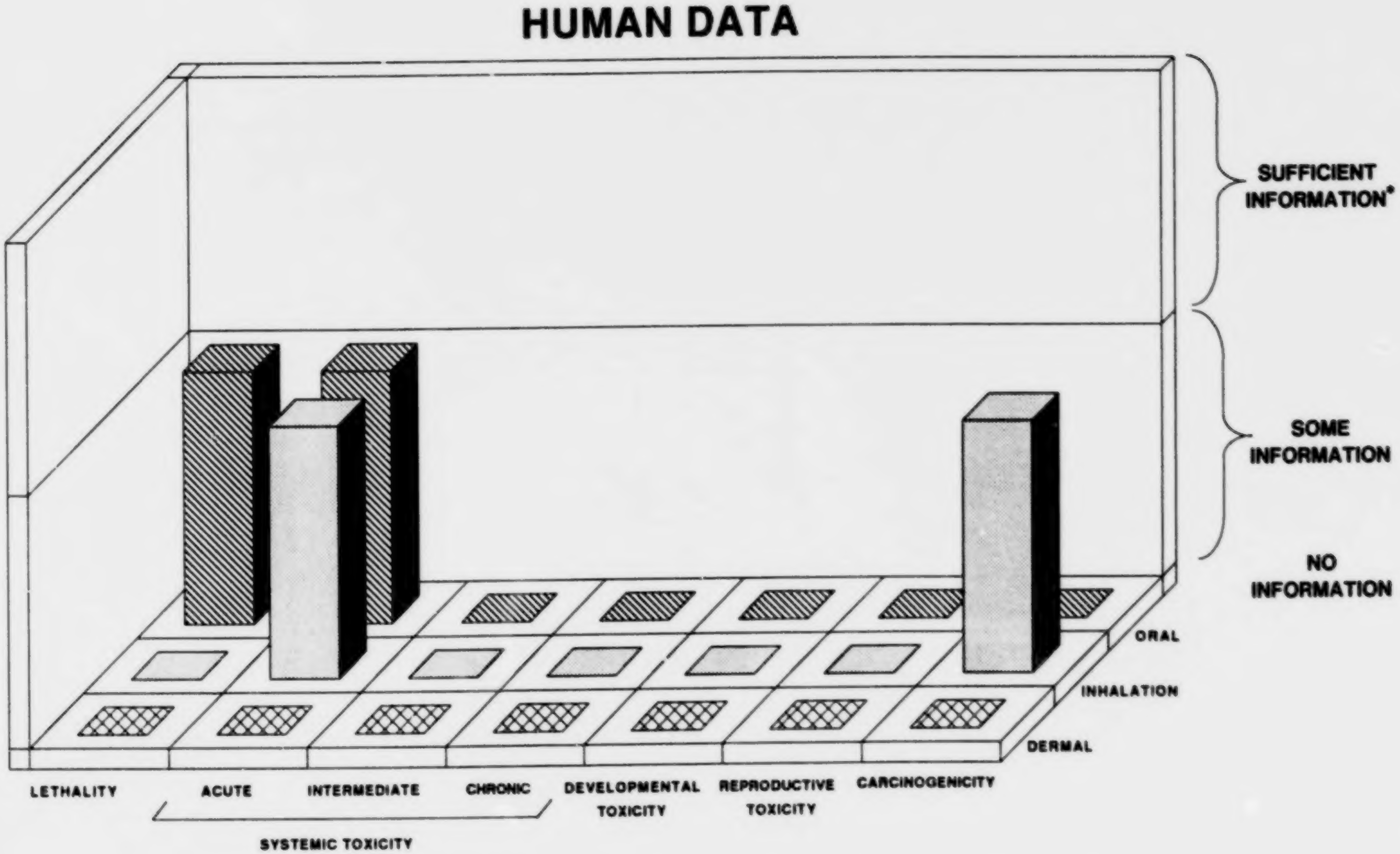
Bars of half height indicate that "some" information for the end point exists, but does not meet any of these criteria.

The absence of a column indicates that no information exists for that end point and route.

2.3.2.2 Description of highlights of graphs

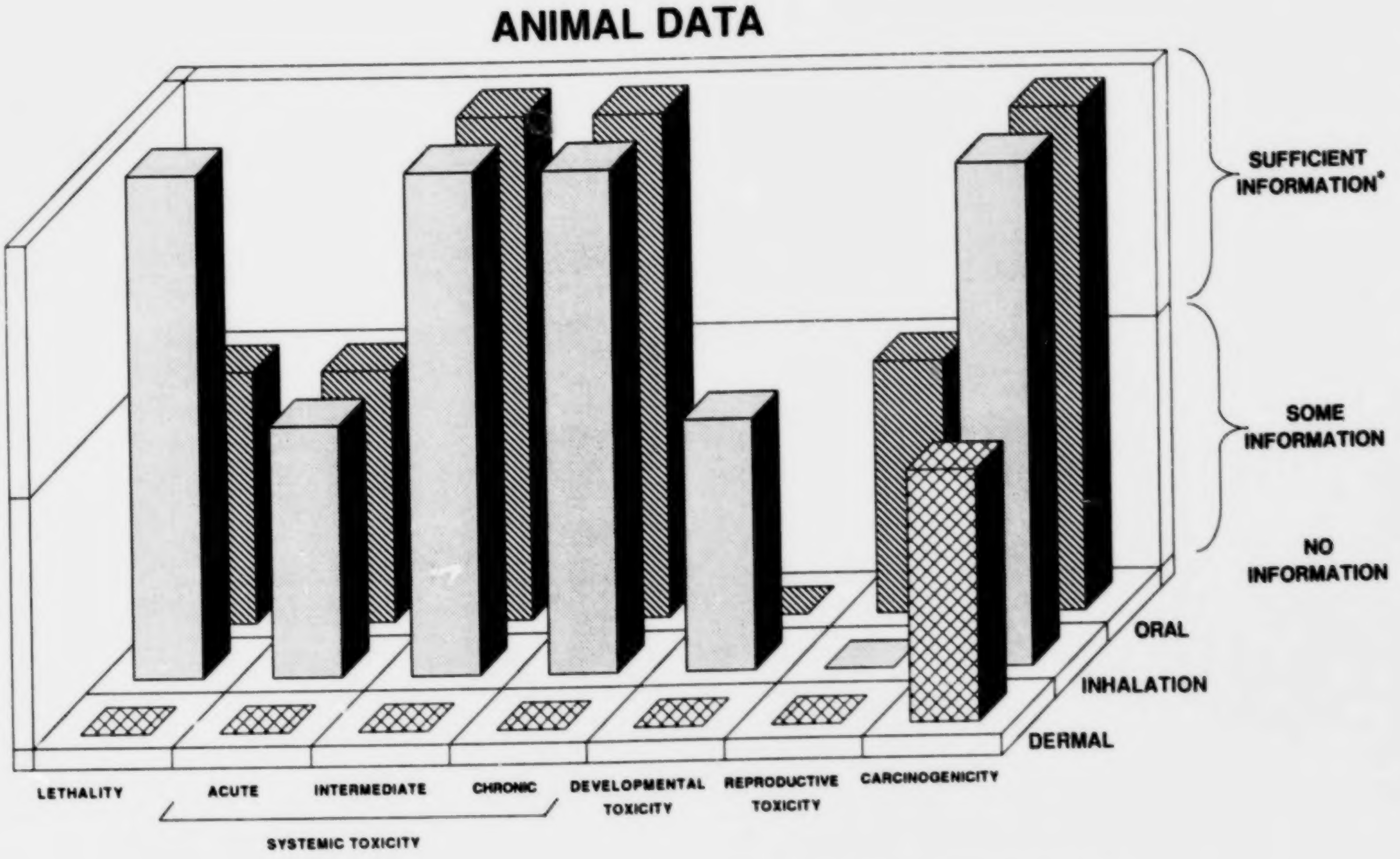
Information regarding effects of acute inhalation exposure of humans to tetrachloroethylene comes from a limited number of studies that primarily evaluated subjective end points. As effects other than to the CNS are poorly characterized and are not associated with exposure levels, and the threshold region for the CNS is incompletely defined, Fig. 2.5 indicates that there are "some" data for systemic effects following acute inhalation exposure. Since the carcinogenicity of inhaled tetrachloroethylene in humans is inconclusive, and doses for acute oral lethality and systemic effects in humans are incompletely characterized, the bars for these end points in Fig. 2.5 also indicate "some" data.

Lethality and systemic effects from oral and inhalation exposure are partially or adequately characterized in animals. Since acute oral doses associated with lethality and target organ/systemic toxicity and



*Sufficient information exists to meet at least one of the criteria for cancer or noncancer end points.

Fig. 2.5. Availability of information on health effects of tetrachloroethylene (human data).



*Sufficient information exists to meet at least one of the criteria for cancer or noncancer end points.

Fig. 2.6. Availability of information on health effects of tetrachloroethylene (animal data).

acute inhalation exposures associated with target organ/systemic toxicity are incompletely characterized, the bars in Fig. 2.6 indicate "some" data. Developmental effects in animals exposed by inhalation are reasonably well established, but additional studies are needed to define an unequivocal NOAEL and to characterize behavioral and teratological effects. Inhalation exposure to tetrachloroethylene caused sperm abnormalities in mice, but the functional significance of this effect has not been established. A single negative study exists on the carcinogenicity of tetrachloroethylene following dermal application of the compound in mice.

2.3.2.3 Summary of relevant ongoing research

Pertinent data regarding relevant ongoing research were not located in the available literature.

2.3.3 Other Information Needed for Human Health Assessment

2.3.3.1 Pharmacokinetics and mechanisms of action

The database for the pharmacokinetics of tetrachloroethylene in animals and humans is fairly adequate. The absorption of tetrachloroethylene following inhalation exposure in humans and animals has been adequately described in several studies (Monster et al. 1979, Pegg et al. 1979, Schumann et al. 1980) and absorption after oral exposure in animals is fairly well characterized (Pegg et al. 1979, Schumann et al. 1980; Frantz and Watanabe 1983). Absorption following oral exposure in humans is, however, based on only one case study (Koppel et al. 1985). Dermal absorption studies are adequate in both humans and animals. Dermal absorption has been studied in humans using whole-body exposure to the vapor (Riihimaki and Pfaffli 1978) and hand and thumb exposure to the liquid (Stewart and Dodd 1964). In animals, dermal absorption of tetrachloroethylene has been studied in guinea pigs (Jakobsen et al. 1982) and mice (Tsuruta 1975). Studies on the distribution of tetrachloroethylene in humans are not adequate. The information on tetrachloroethylene distribution in humans presented in this document is drawn largely from physiologically based pharmacokinetic (PB-PK) models and not from actual experimental data. Data on the metabolism of tetrachloroethylene in humans and animals is fairly adequate. The pathways of tetrachloroethylene metabolism remain speculative, however, and a study by Dekant et al. (1985) raises the possibility of new metabolic pathways in animals. Excretion of tetrachloroethylene and metabolites has been adequately described in humans by Monster et al. (1979) and in animals by Pegg et al. (1979), Schumann et al. (1980), and Frantz and Watanabe (1983).

2.3.3.2 Monitoring of human biological samples

Monitoring human biological samples for exposure to tetrachloroethylene has been adequately described for both occupationally and nonoccupationally exposed individuals. Monitoring tetrachloroethylene in the exhaled air of nonoccupationally exposed individuals has been described by Krotoszynski et al. (1979), Wallace (1986), and Monster and Smolders (1984). Monitoring for tetrachloroethylene exposure in workers, using samples of exhaled air, blood, and urine, has been described by

Monster et al. (1983). Several gas chromatographic methods for measuring tetrachloroethylene and metabolites in biological samples have been described in the literature (Ramsey and Flanagan 1982, Ziglio et al. 1984). In addition, Bagnell et al. (1977) reported measuring tetrachloroethylene in breast milk using headspace gas chromatography and Ghantous (1986) has reported measuring trichloroacetic acid (a tetrachloroethylene metabolite) in the amniotic fluid of mice.

2.3.3.3 Environmental considerations

Methodology of sufficient sensitivity and specificity exists to measure tetrachloroethylene in the environment.

The bioavailability of tetrachloroethylene from environmental media (soil, water, and air) appears to be reasonably well understood.

There appears to be a reasonably good understanding of the environmental fate and transport of tetrachloroethylene.

No studies were found involving the environmental interaction of tetrachloroethylene with other co-contaminants. There are no known ongoing experimental studies pertaining to the environmental fate of tetrachloroethylene.

3. CHEMICAL AND PHYSICAL INFORMATION

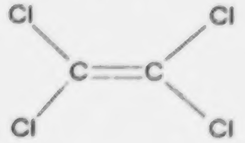
3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of tetrachloroethylene are listed in Table 3.1. Tetrachloroethylene is referred to as perchloroethylene in a significant percentage of the published literature.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of tetrachloroethylene are presented in Table 3.2.

Table 3.1. Chemical identity of tetrachloroethylene

Chemical name	Ethene, tetrachloro-	CAS (10th Collective Index)[a]
Synonyms	1,1,2,2-Tetrachloroethylene; tetrachloroethylene; perchloroethylene; perc; ethylene tetrachloride; per; perchlor; perchlorethylene; perk	IARC 1979
Trade names	Ankilostin; Antisall; Dee-Solv; Didakene; Dow-Per; ENT 1860; Fedal-Un; Nema perclene; percosolv; perklone; persec; tetlen; tetracap; tetraleno; tetravec, tetroquer; tetropil	IARC 1979
Chemical formula	C_2Cl_4	SANSS 1987
Wiswesser line notation	GYGUYGG	HSDB 1987
Chemical structure		SANSS 1987
Identification Nos.		
CAS Registry No.	127-18-4	SANSS 1987
NIOSH RTECS No.	KX3850000	SANSS 1987
EPA Hazardous Waste No.	U210	HSDB 1987
OHM-TADS No.	7216847	HSDB 1987
DOT/UN/INCO Shipping No.	UN1897; IMCO 6.1	HSDB 1987
STCC No.	49 403 55	HSDB 1987
Hazardous Substance Data Bank No.	124	HSDB 1987
National Cancer Institute No.	NCI-C04580	SANSS 1987

[a] Chemical Abstracts Service.

Table 3.2. Physical and chemical properties of tetrachloroethylene

Property	Value	References
Molecular weight	165.83	Keil 1979
Color	Colorless	Sax and Lewis 1987
Physical state	Liquid (at room temperature)	Sax and Lewis 1987
Odor	Ether-like odor	EPA 1985a
Freezing point	−22.7°C	Keil 1979
Boiling point	121.2°C (at 760 mm Hg)	Keil 1979
Autoignition temperature	Unknown	
Solubility		
Water	150 mg/L at 25°C	Keil 1979
Organic solvents	Miscible with ethanol, diethyl ether, and oils in all proportions	Sax and Lewis 1987
Specific gravity	1.62 (20/4°C)	Keil 1979
Partition coefficients		
Log octanol-water	2.88	Hansch and Leo 1981
Vapor pressure	14 mm Hg at 20°C 24 mm Hg at 30°C	Verschueren 1983
Henry's law constant	0.82 unitless	Pearson and McConnell 1975
Refractive index	1.5029 at 25°C	Sax and Lewis 1987
Flash point	None	Sax and Lewis 1987
Flammable limits	Nonflammable	Sax and Lewis 1987
Conversion factors		
Air	1 ppm = 6.89 mg/m^3 (20°C) 1 mg/m^3 = 0.15 ppm	Verschueren 1983
Water	1 ppm (w/v) = 1 mg/L = 1 μg/mL	

4. TOXICOLOGICAL DATA

4.1 OVERVIEW

Tetrachloroethylene is readily absorbed following inhalation exposure. Absorption of tetrachloroethylene following ingestion is also rapid and nearly complete. Peak blood levels of tetrachloroethylene are reached within 1 h following oral administration of the compound in both humans and animals. In contrast to the extensive absorption of tetrachloroethylene following inhalation or oral exposure, absorption of the chemical following dermal exposure is poor.

The adipose tissue appears to be the primary site of tetrachloroethylene distribution following absorption in both humans and animals. Little information is available regarding the distribution of tetrachloroethylene following inhalation exposure in humans. Several investigators have, however, constructed physiologically based pharmacokinetic (PB-PK) models, and these models predict that a large percentage of an absorbed dose of tetrachloroethylene in humans is distributed to the fat tissue.

The principal site of tetrachloroethylene metabolism is the liver, where it is transformed to trichloroacetic acid by the hepatic cytochrome P-450 system. Many investigators have postulated the initial formation of an epoxide. It is generally accepted that the metabolites of tetrachloroethylene, of which trichloroacetic acid is the most prominent, are the agents responsible for the toxic effects. Metabolism of tetrachloroethylene in humans is limited, i.e., saturation occurs at relatively low levels of exposure, implying that risk may not increase linearly with exposure.

The metabolic pathways for tetrachloroethylene metabolism appear to be different in humans and animals. The primary urinary metabolite found in tetrachloroethylene-exposed humans is trichloroacetic acid, although trichloroethanol has also been identified. These same metabolites are also found in the urine of tetrachloroethylene-exposed animals; in addition, oxalic acid is an important metabolite in rats, but has not been reported in humans. Tetrachloroethylene metabolism has been demonstrated to be dose-dependent (i.e., saturable) in rats and mice, and for these two species metabolism of tetrachloroethylene appears to be proportional to body surface area, rather than to body weight.

The main excretion pathway of an absorbed dose of tetrachloroethylene in both animals and humans is through exhalation of the unmetabolized parent compound. The urinary excretion of metabolites accounts for only a small percentage of the absorbed dose, except in mice, a species in which urinary excretion of metabolites is considerable.

Limited acute toxicity data indicate that tetrachloroethylene is relatively nontoxic by the inhalation and oral routes. A 4-h LC50 of 5,200 ppm for mice and a single-dose LD50 of 3,005 mg/kg for rats have been reported. Ingestion of ~60 to 86 mg of tetrachloroethylene per kg of body weight by humans for antihelminthic medication was reported to be nonlethal.

The principal target organs of tetrachloroethylene toxicity are the CNS, liver, and kidneys. Interpretation of the available data is complicated by differences in species, exposure schedules, and end points, but the CNS and liver appear to be the most sensitive targets. Continuous-inhalation exposure for 30 days induced hepatic effects in mice at concentrations as low as 9 ppm; CNS effects in gerbils occurred at concentrations as low as 60 ppm, when exposed for 3 to 12 months. Short-term inhalation studies indicate that the threshold for CNS effects in humans is in the range of 100 to 200 ppm.

Limited oral toxicity data are available, but subchronic exposure to doses >100 mg/kg/day produced hepatic effects in mice and rats.

Fetotoxic effects, including skeletal ossification anomalies, occurred in mice and rats exposed to ≥300 ppm tetrachloroethylene by inhalation, but teratogenic effects were not observed. Subtle effects on behavioral performance and brain neurochemistry in the offspring of mice were associated with gestational exposure to 900 ppm. Oral teratogenicity data are not available.

There is little information concerning reproductive effects of tetrachloroethylene. A short-term inhalation study suggests that tetrachloroethylene may cause sperm abnormalities in mice but not rats.

The genotoxicity of tetrachloroethylene has been studied using a variety of assays in both in vivo and in vitro test systems. The results of these tests were largely negative. A few positive genotoxic responses using tetrachloroethylene were reported, although problems related to the purity of the test compound or the design of the assay raise questions regarding the interpretation of the results.

Some epidemiological studies suggest a possible association between chronic tetrachloroethylene exposure and increased cancer risk, but confounding factors (particularly exposure to other chemicals) and study limitations make the association inconclusive. Chronic inhalation exposure to tetrachloroethylene produced increased incidences of mononuclear cell leukemia in rats, kidney tumors in male rats only, and hepatocellular adenomas and carcinomas in mice. Although the increased incidence in kidney tumors in male rats was not statistically significant, this type of tumor is considered rare. Chronic oral exposure to tetrachloroethylene produced increased incidences of hepatocellular carcinomas in mice. A primary metabolite of tetrachloroethylene, trichloroacetic acid, and a minor metabolite, dichloroacetic acid, have been shown to induce liver cancer in B6C3F1 mice (Herren-Freund et al. 1987). Also, metabolism in rat kidney has been shown to produce a mutagenic cysteine conjugate in the kidney (Anders et al. 1988, Dekant et al. 1986).

4.2 TOXICOKINETICS

4.2.1 Absorption

4.2.1.1 Inhalation

Human. The primary route of exposure to tetrachloroethylene is inhalation. Tetrachloroethylene is readily absorbed by humans through the lungs into the blood, and pulmonary uptake of tetrachloroethylene is proportional to ventilation rate, duration of exposure, and (at lower atmospheric concentrations of tetrachloroethylene) to the concentration of tetrachloroethylene in the inspired air (Hake and Stewart 1977). Monster et al. (1979) measured the uptake of tetrachloroethylene in male volunteers exposed to concentrations between 72 and 144 ppm for 4 h. The data indicated that uptake was influenced more by lean body mass than by ventilation rate or the amount of adipose tissue, and that uptake decreased as a function of exposure time so that after 4 h it was 75% of its initial value. This latter finding may be attributable to a large percentage uptake of tetrachloroethylene during the first few minutes of exposure or the decreased uptake may be due to a decrease in retention of tetrachloroethylene with exposure time.

Animal. Inhalation experiments in animals indicate that tetrachloroethylene is readily absorbed through the lungs and into the blood. Although the pulmonary absorption of tetrachloroethylene has not been demonstrated to be directly proportional to atmospheric tetrachloroethylene concentration, Pegg et al. (1979) have shown that the amount of tetrachloroethylene absorbed in male Sprague-Dawley rats exposed for 6 h increases over atmospheric tetrachloroethylene concentration ranges of between 10 and 600 ppm. Radioactive label has been detected in the urine, feces, expired air, and carcasses of mice following inhalation exposure to 10 ppm of radiolabeled tetrachloroethylene for 6 h (Schumann et al. 1980).

4.2.1.2 Oral

Human. Tetrachloroethylene was found in the blood of a 6-year-old boy who ingested 12 to 16 g of the compound, indicating that tetrachloroethylene is absorbed following oral administration in humans (Koppel et al. 1985). The initial blood tetrachloroethylene level was 21.5 μg/mL 1 h after ingestion.

Animal. Results from several studies (Pegg et al. 1979, Schumann et al. 1980, Frantz and Watanabe 1983) indicate that tetrachloroethylene is rapidly and virtually completely absorbed following oral administration to both rats and mice. A peak blood tetrachloroethylene concentration of 40 μg/mL was measured 1 h following administration of the chemical by gavage (500 mg/kg) to rats (Pegg et al. 1979). The analytical technique used in this study (Pegg et al. 1979) lacked the sensitivity for precisely measuring blood levels of tetrachloroethylene following administration of 1 mg/kg of the compound.

4.2.1.3 Dermal

Human. Dermal absorption of vapors of tetrachloroethylene in humans is apparently insignificant. Riihimaki and Pfaffli (1978) compared dermal and pulmonary absorption of tetrachloroethylene vapor by exposing subjects to the vapor (600 ppm) after they had been fitted with a full-facepiece respirator to prevent inhalation. After an exposure period of 3.5 h, absorption of tetrachloroethylene by the dermal route was found to be 1% of that expected had no respirator been worn. Stewart and Dodd (1964) measured dermal absorption of tetrachloroethylene by immersing one thumb of an experimental subject (~0.1% of the total body surface area) into a liquid sample and then measuring the concentration of tetrachloroethylene in the exhaled air. A peak concentration of 0.31 ppm in exhaled air was reached after 40 min of exposure.

Animal. As in humans, dermal absorption of tetrachloroethylene in animals also appears to be poor (EPA 1985a). Jakobson et al. (1982) studied absorption following application of the undiluted compound to the shaved backs of guinea pigs. The blood concentration of the compound reached a peak of 1.1 μg/mL after 30 min of exposure and then decreased to 0.63 μg/mL after 6 h of exposure. The decline in tetrachloroethylene blood levels with duration of exposure was attributed to local vasoconstriction of the exposed skin or rapid transport of the compound from the blood to adipose tissue. The decrease in blood concentration with exposure time was not attributed to rapid metabolism of the compound because little of the absorbed dose was expected to be metabolized in this species.

Tsuruta (1975) applied tetrachloroethylene to a patch of abdominal skin of mice for 15 min and reported that the in vivo dermal absorption was 0.24 $mg/cm^2/h$. An in vitro study using excised rat skin demonstrated that the rate of penetration by tetrachloroethylene was much slower than that of several other halogenated hydrocarbons (i.e., 2,070 times slower than that of the fastest compound, dichloromethane), and the measured rate for tetrachloroethylene penetration was 0.0055 $mg/cm^2/h$ (Tsuruta 1977).

4.2.2 Distribution

4.2.2.1 Inhalation

Human. The distribution of tetrachloroethylene following inhalation exposure in humans has not been extensively studied, but a number of investigators (Guberan and Fernandez 1974, Chen and Blancato 1987) have constructed physiologically based pharmacokinetic (PB-PK) models for tetrachloroethylene distribution using pharmacokinetic and metabolic information derived from human studies.

An experimental indication that tetrachloroethylene is accumulated in the body is provided by the study of Stewart et al. (1970). Experimental subjects were exposed by inhalation to 100 ppm tetrachloroethylene 7 h/day for 5 days. During the 5-day exposure period, the concentration of tetrachloroethylene in exhaled breath increased as the 5-day week progressed, indicating an increase in the body burden with repeated daily exposures. Following termination of exposure, a slight but definite accumulation of the compound was indicated by a long decay (>14 days) of the concentration of tetrachloroethylene in exhaled air.

The PB-PK model for tetrachloroethylene distribution developed by Guberan and Fernandez (1974) divides the body into four physiological compartments on the basis of the amount of blood flow to each of the compartments. The compartments were: a blood-vessel-rich group of tissues (corresponding to brain, heart, hepatoportal system, kidneys, and endocrine glands), a muscle group (muscle and skin), a fat group (adipose tissue and yellow marrow), and a vessel-poor group composed of connective tissue (e.g., bone and cartilage). This model predicts that an 8-h exposure of humans to 100 ppm tetrachloroethylene would result in a body burden of 1,000 mg tetrachloroethylene for a 70-kg person, and half of this body burden would be distributed to the fat tissue.

Animal. As predicted for humans, tetrachloroethylene is distributed readily to the fat compartment of animals. The distribution of the compound in Sprague-Dawley rats following exposure to 200 ppm tetrachloroethylene vapor for 5 days was characterized by Savolainen et al. (1977). Seventeen hours after the fourth daily exposure, tetrachloroethylene was found to have distributed primarily to adipose tissue and especially the perirenal fat (tetrachloroethylene levels were 145 times greater in the perirenal fat than those measured in blood). Tetrachloroethylene levels in the brain and liver were approximately five times greater than those found in blood.

Tetrachloroethylene also appears to be able to cross the placenta and distribute to the fetus and amniotic fluid. Unmetabolized tetrachloroethylene was found in the fetoplacental unit following inhalation exposure of pregnant mice for 10 min or 1 h to radioactive tetrachloroethylene (Ghantous et al. 1986). High uptake of radioactivity in maternal tissues was found in the body fat, brain, nasal mucosa, blood, and in well-perfused organs such as the liver, kidneys, and lungs.

4.2.2.2 Oral

Human. Pertinent data regarding the distribution of tetrachloroethylene in humans following oral administration were not found in the available literature.

Animal. Vemmer et al. (1984) reported that after gavage administration of tetrachloroethylene to pigs, the chemical was concentrated mainly in subcutaneous fat.

4.2.2.3 Dermal

Pertinent data regarding the distribution of tetrachloroethylene in both humans and animals following dermal exposure to the compound were not found in the available literature.

4.2.3 Metabolism

Since a key aspect of the nephrotoxicity of tetrachloroethylene relates to the metabolic formation of a glutathione *S*-conjugate, a brief description of the mechanisms involved is presented below.

Cytosolic and microsomal fractions of rat liver metabolize tetrachloroethylene into *S*-(1,2,2-trichlorovinyl)glutathione. The conjugates formed in the liver are then transported into plasma and bile. γ-Glutamyltransferase, which is localized in the outer surface of the renal proximal tubules and on the biliary ductular epithelium, catalyzes the formation of a cysteine *S*-conjugate. The latter is filtrated and taken up across the brush-border membrane into renal proximal tubular cells where it can be detoxified by conversion to the mercapturic acid. It also may be metabolized by β-lyase to an unstable thiol that leads to the formation of toxic products (Anders et al. 1988).

4.2.3.1 Inhalation

Human. Following inhalation of tetrachloroethylene in humans, the primary metabolites identified in urine and blood were trichloroacetic acid and trichloroethanol. Using gas chromatography, Monster (1986) was able to detect trichloroacetic acid in the urine and blood of workers exposed to tetrachloroethylene at concentrations of 10 to 30 ppm in dry-cleaning or metal-cleaning shops. A small amount of trichloroethanol was also detected in the urine, but the possibility that trichloroethanol was a potential air contaminant was not ruled out. The detection of TCE as a metabolite of tetrachloroethylene in humans is apparently dependent on the analytical method used. Earlier studies (Monster et al. 1979, Hake and Stewart 1977) did not report the presence of TCE in the urine of tetrachloroethylene-exposed subjects, but this may have been because a colorometric method (Fujiwara reaction) was used to measure urinary tetrachloroethylene metabolites. The metabolism of tetrachloroethylene is saturable in humans following inhalation exposure (Ohtsuki et al. 1983). Ohtsuki et al. (1983) measured total trichloro compounds in the urine of tetrachloroethylene-exposed workers in dry-cleaning and textile-processing plants. The total trichloro-compound concentration reached a plateau in the urine at tetrachloroethylene exposure concentrations of >100 ppm in the air. This suggests that the capacity of humans to metabolize tetrachloroethylene is limited. Thioethers have also been detected in the urine of dry-cleaning workshop employees, but the significance of this finding is unclear (Lafuente and Mallol 1986).

Animal. Oxalic acid was determined to be the primary urinary metabolite of tetrachloroethylene in rats exposed by inhalation to the compound for 6 h (Pegg et al. 1979). Oxalic acid concentrations in the urine of rats exposed to either 10 or 600 ppm tetrachloroethylene were 0.27 and 2.37 μmol/mL, respectively. Tetrachloroethylene and TCA were not detected in the urine of rats exposed to tetrachloroethylene at the above concentrations.

4.2.3.2 Oral

Human. TCE, TCA, and trace amounts of unmetabolized tetrachloroethylene were detected in the urine of a child who drank 8 to 10 mL of pure tetrachloroethylene (Koppel et al. 1985).

Animal. Data regarding the urinary metabolites of tetrachloroethylene in rodents exposed by the oral route are conflicting. Buben and O'Flaherty (1985) reported that the only metabolite in the urine of tetrachloroethylene-exposed mice was TCA. Swiss-Cox mice were administered tetrachloroethylene in doses of 0, 20, 100, 200, 500, 1,000, 1,500 and 2,000 mg/kg/day in corn oil by gavage for 6 weeks. The amount of total metabolites found in the urine increased logarithmically with dose and approached a plateau with doses of tetrachloroethylene higher than 1,000 mg/kg/day. This indicates that the formation of metabolites (and probably overall tetrachloroethylene metabolism) is capacity-limited. Exposure to oral doses of 500 mg/kg ^{14}C-tetrachloroethylene results in saturation of the oxidative metabolism in both the rat and the mouse (Pegg et al. 1979, Schumann et al. 1980). Oxalic acid was the primary urinary metabolite in rats exposed to tetrachloroethylene in corn oil by gavage (Pegg et al. 1979). Rats exposed by gavage to either 1 or 500 mg/kg tetrachloroethylene had urinary oxalic acid concentrations of 0.13 and 2.74 µmol/mL, respectively, in urine samples collected 12 h following exposure. Tetrachloroethylene and TCA acid were not detected in the urine in this study. Seven metabolites of tetrachloroethylene were found in the urine of rats and mice given a single oral dose (vehicle not stated) of 800 mg/kg tetrachloroethylene (Dekant et al. 1985). Using high-performance liquid chromatography (HPLC), radio gas chromatography (GC), and gas chromatography/mass spectrometry (GC/MS), Dekant et al. (1985) detected oxalic acid, *N*-oxalylaminoethanol, dichloroacetic acid, TCA, *N*-trichloracetylaminoethanol, free and conjugated TCE, and an unidentified metabolite. However, the authors did not state whether the metabolite patterns were the same for rats and mice.

The metabolism of tetrachloroethylene is believed to be mediated by a cytochrome P-450 catalyzed oxidation reaction involving the formation of an epoxide intermediate. Evidence for the involvement of hepatic microsomal cytochrome P-450 during the in vitro metabolism of tetrachloroethylene was provided in the study by Costa and Ivanetich (1980). This evidence included production of a type I difference spectrum (indicating tetrachloroethylene binding to cytochrome P-450), production of known metabolites of tetrachloroethylene following its incubation with hepatic microsomes and NADPH, and inhibition of spectral binding and of formation of metabolites by cytochrome P-450 inhibitors. Many investigators (Buben and O'Flaherty 1985, Daniel 1963, Henschler 1977, Leibman and Ortiz 1977, Yllner 1961) have postulated that an epoxide is initially formed following interaction of tetrachloroethylene with the cytochrome P-450 system, but as with other substrates for this system, current technology does not permit the isolation of an epoxide intermediate.

4.2.3.3 Dermal

Pertinent data regarding dermal exposure in humans and animals were not found in the available literature.

4.2.4 Excretion

Exhalation of unmetabolized parent compound appears to be the primary route of excretion of an absorbed dose of tetrachloroethylene in humans, regardless of the route of exposure.

4.2.4.1 Inhalation

Human. In volunteers exposed by inhalation for 4 h to either 72 or 144 ppm tetrachloroethylene, most (80 to 100%) of the total uptake was excreted by the lungs unchanged (Monster et al. 1979). Similar findings were reported by Hake et al. (1976). From concentration-time course curves of tetrachloroethylene in the exhaled air and blood, the half-lives of tetrachloroethylene in three major body compartments were calculated to be 12 to 16 h, 30 to 40 h, and 55 h for the vessel-rich group, muscle group, and adipose group, respectively. Tetrachloroethylene was postulated to have a long half-life in adipose tissue because of its high adipose/blood partition coefficient and because of the relatively low rate of blood perfusion to this tissue.

The urinary excretion of metabolites of tetrachloroethylene represents a small percentage of the absorbed dose of tetrachloroethylene following inhalation exposure. Urinary excretion of TCA represented <1% of the total estimated absorbed dose of tetrachloroethylene in volunteers exposed by inhalation to 72 or 144 ppm for 4 h (Monster et al. 1979). Ohtsuki et al. (1983) calculated that 2% of the tetrachloroethylene absorbed through the lungs following an 8-h exposure to 50 ppm tetrachloroethylene would be metabolized and excreted in the urine. A large part (38%) of the absorbed dose would be exhaled unchanged. Ikeda et al. (1972) reported that the urinary excretion of trichloroethanol and trichloroacetic acid in human volunteers increased linearly with tetrachloroethylene concentrations in the air of up to 50 ppm, but reached a plateau with higher concentrations. This indicates that the metabolism of tetrachloroethylene is saturable and that the concentration of urinary metabolites does not necessarily reflect the degree of exposure. The biological half-life of urinary metabolites of tetrachloroethylene was 144 h in occupationally exposed individuals (Ikeda and Imamura 1973). Ogata et al. (1971) determined that 67 h after a 3-h exposure to tetrachloroethylene vapors, the excretion of trichloroacetic acid in the urine of human volunteers was 1.8% of the estimated tetrachloroethylene retained. Dry-cleaning workshop employees showed an increased trend of excretion of thioethers throughout the week, but the significance of this finding is unclear since the levels of thioethers were well within the range found in unexposed individuals (Lafuente and Mallol 1986). In a case of accidental exposure reported by Weiss (1969), excretion of trichloroacetic acid had marked daily fluctuations.

Animal. The relative importance of the routes of excretion of tetrachloroethylene and metabolites following inhalation exposure in animals appears to depend on the dose and the species. Following a 6-h inhalation exposure in rats to 10 ppm radiolabeled tetrachloroethylene, the parent compound (68% of the absorbed dose) and radiolabeled carbon dioxide (3.6% of the absorbed dose) were excreted in the exhaled air over a 72-h period (Pegg et al. 1979); 24% of the absorbed dose was excreted as nonvolatile metabolites in urine and feces, and 3 to 4% remained in the carcass 72 h after exposure. When the exposure concentration was increased to 600 ppm in this study, the percentage of the absorbed dose exhaled as unmetabolized parent compound over a 72-h period increased to 88%. At this higher exposure level (600 ppm), 9% of the absorbed dose was excreted in the urine and feces and 2% remained in the carcass. In contrast to rats, mice appeared to excrete most of an absorbed dose of inhaled tetrachloroethylene as metabolites in the urine. In mice exposed to the relatively low concentration of 10 ppm of radiolabeled tetrachloroethylene for 6 h, 12% of the absorbed dose was excreted as unmetabolized compound in the expired air in a 72-h follow-up period (Schumann et al. 1980). Most of the absorbed radioactivity was excreted in the urine as metabolites. Mice were not exposed to higher concentrations in this study. In a study by Yllner (1961), female mice exposed for 2 h to ^{14}C-tetrachloroethylene vapors at 1.3 mg/g body weight (approximately 150 ppm) absorbed 70% of the dose. In 4 days, 90% of the absorbed radioactivity was excreted, 70% in expired air, 20% in the urine, and <0.5% in the feces. Trichloroacetic acid and oxalic acid composed 52 and 11% of the label in the urine, respectively. Traces of dichloroacetic acid were also present. The apparent disagreement between the results of Yllner (1961) and those of Schumann et al. (1980) regarding the percentage of unchanged tetrachloroethylene in the expired air demonstrates that as the body burden of tetrachloroethylene increases, the percentage excreted unchanged increases. This observation suggests that the metabolism of tetrachloroethylene and urinary excretion of metabolites in rodents in general are rate-limited and dose-dependent.

4.2.4.2 Oral

Human. The only study of the excretion of tetrachloroethylene and metabolites following oral exposure in humans is a case report of a 6-year-old boy who accidently ingested 8 to 10 mL of the compound (Koppel et al. 1985). The bulk of the ingested tetrachloroethylene was eliminated by the lungs; however, this was not under normal conditions since the patient was hyperventilated to facilitate pulmonary elimination of the compound. Tetrachloroethylene, TCA, and TCE were detected and quantified in the urine. Total urinary tetrachloroethylene decreased from 30 μg on day 1 of treatment to 3 μg on day 3. Total urinary trichloro compounds increased from 8 mg on day 1 to 68 mg on day 3.

Animal. Exhalation of unchanged tetrachloroethylene was determined to be the main route of excretion of the orally administered chemical (Pegg et al. 1979, Schumann et al. 1980, Frantz and Watanabe 1983). Rats given a single oral dose of tetrachloroethylene (1 mg/kg) excreted 72% of the absorbed dose as unmetabolized in the breath and 16% as metabolites in the urine over a 72-h period (Pegg et al. 1979). When the administered dose was increased to 500 mg/kg, the percentage of the dose exhaled as unmetabolized parent compound over a 72-h period increased to 90%, whereas the percentage of the dose excreted as metabolites in the urine dropped to 5%. Similar results were reported in rats following ingestion of tetrachloroethylene-saturated drinking water solutions ad libitum for 12 h (Frantz and Watanabe 1983). Administration of tetrachloroethylene in the drinking water provided a dose (~8 mg/kg) that was somewhat lower than the doses of tetrachloroethylene given in gavage studies. Excretion of the absorbed dose was similar, however, for both methods of oral administration. Of the absorbed dose, 88% was exhaled as unmetabolized parent compound over a 72-h period in this drinking water study (Frantz and Watanabe 1983), and 7.2% of the absorbed radioactivity was found in the urine. Exhalation of unmetabolized tetrachloroethylene was also the predominant mode of excretion of an orally administered tetrachloroethylene dose in mice. Mice given a single oral dose of tetrachloroethylene (500 mg/kg) excreted 83% of the absorbed dose as unmetabolized in the expired air (Schumann et al. 1980); 10% appeared as metabolites in the urine.

4.2.4.3 Dermal

Human. Human volunteers who immersed their thumbs for 30 min in liquid tetrachloroethylene exhaled the compound unchanged for time periods exceeding 5 h (Stewart and Dodd 1964). The maximum mean alveolar air concentration of tetrachloroethylene in these subjects was 0.3 ppm, and the authors were able to construct concentration-time curves for the mean alveolar tetrachloroethylene concentrations.

Animal. Pertinent data regarding the excretion of tetrachloroethylene and metabolites following dermal exposure in animals were not found in the available literature.

4.3 TOXICITY

4.3.1 Lethality and Decreased Longevity

4.3.1.1 Inhalation

Human. Deaths caused by tetrachloroethylene inhalation have been reported in the literature. A 33-year-old male was found unconcious after performing work on a plugged line in a commercial dry-cleaning establishment (Lukaszewski 1979). Exposure to tetrachloroethylene was presumably by inhalation, since an autopsy revealed no tetrachloroethylene in the stomach contents, but high levels of the compound in the blood and brain (4.4 mg/100 ml and 36 mg/100 g, respectively). In addition, Levine et al. (1980) reported that a 53-year-old male dry cleaner was found dead at the scene after being overcome by tetrachloroethylene fumes.

Animal. A 4-h inhalation LC_{50} of 5,200 ppm for mice has been reported (Friberg et al. 1953). Data used to derive the LC_{50} show that the highest concentration for a 4-h exposure that did not produce death in mice was 2,450 ppm; the lowest concentration to produce death was 3,000 ppm. In prechronic NTP (1986) studies, the highest concentration for a 4-h exposure that did not produce death in mice or rats was 2,445 ppm; the lowest concentrations producing death were 2,613 ppm in mice and 3,786 ppm in rats. Rowe et al. (1952) reported that a single 10- or 14-h exposure to 2,000 ppm and a single 4-h exposure to 3,000 ppm did not produce mortality in rats, and that exposure to 3,000 ppm for 5 h or longer produced some mortality.

Rats and mice were exposed to tetrachloroethylene by inhalation for 6 h/day, 5 days/week for 14 days or 13 weeks in other prechronic NTP (1986) studies. The highest concentration not producing death and the lowest concentration producing death were 875 and 1,750 ppm, respectively, in rats in the 14-day study and 800 and 1,600 ppm, respectively, in rats and mice in the 13-week study. A recent abstract indicates that continuous exposure to 800 ppm for 12 weeks produced 70% mortality in rats (Nomiyama et al. 1986).

Rats were exposed to 200 or 400 ppm and mice were exposed to 100 or 200 ppm tetrachloroethylene for 6 h/day, 5 days/week for 103 weeks in an NTP (1986) carcinogenesis bioassay. Increased mortality occurred in high-dose male rats at week 102 (39/50 compared to 27/50 in controls), in male mice after 74 to 78 weeks (25/50 at 100 ppm and 18/50 at 200 ppm compared to 3/50 in controls), and in female mice after 90 weeks (17/50 at 100 ppm and 30/50 at 200 ppm compared to 11/50 in controls).

4.3.1.2 Oral

Human. Oral doses of tetrachloroethylene between 4.5 and 6.5 g have been reported as effective and safe in the treatment of hookworms, with inebriation being the only side effect observed in 46,000 treated patients (Lambert 1933). One death following human ingestion of 3 mL of tetrachloroethylene has been reported in the literature (Chaudhuri and Mukerji 1947). An autopsy revealed acute hemorrhagic enteritis.

Animal. Single-dose 14-day LD_{50} values of 3,835 and 3,005 mg/kg were determined for male and female rats treated via stomach tube (Hayes et al. 1986). Tremors, ataxia, and CNS depression preceded death in the Hayes et al. (1986) study, but necropsy findings were unremarkable except for hemorrhagic lungs and adrenals in some animals. An oral LD_{50} of 8,100 mg/kg was reported for mice (Wenzel and Gibson 1951).

In prechronic studies for an NCI (1977) carcinogenicity bioassay, groups of five Osborne-Mendel rats of each sex were treated with tetrachloroethylene in corn oil by gavage at doses of 316, 562, 1,000, 1,780, or 3,160 mg/kg 5 days/week for 6 weeks followed by 2 weeks of observation. Deaths (numbers unspecified) occurred in both males and females at the two highest doses but not at ≤1,000 mg/kg. Mice were treated with doses of 562 to 5,620 mg/kg according to the same schedule, but survival data were not reported.

For chronic exposure, effects on survival were observed in NCI (1977) gavage studies with rats and mice. In rats, time-weighted average (TWA) doses of 471 and 941 mg/kg/day in males and 474 and 949 mg/kg/day in females for 78 weeks followed by 32 weeks of observation resulted in dose-related decreased survival. In mice, TWA doses of 450 and 550 mg/kg/day in males and 300 and 400 mg/kg/day in females for 78 weeks followed by 12 weeks of observation resulted in decreased survival. The decreased longevity may have been due to toxic nephropathy in both species and/or hepatocellular carcinomas in mice. The lowest TWA dose, 300 mg/kg/day in mice, is indicated as an FEL for decreased longevity in Figs. 2.2 and 2.5.

4.3.1.3 Dermal

Pertinent data regarding the lethality of tetrachloroethylene following dermal exposure in animals and humans were not found in the available literature.

4.3.2 Systemic/Target Organ Toxicity

4.3.2.1 Neurological and behavioral effects

Inhalation, human. Rowe et al. (1952) collected subjective reports from persons exposed to tetrachloroethylene concentrations ranging from 106 to 1,060 ppm in single exposures. At the lowest concentration, no significant adverse CNS effects were noted in six subjects after 1 h of exposure, although slight irritation of the eyes was experienced. Of four subjects exposed to 216 ppm tetrachloroethylene for 45 min to 2 h, two subjects experienced dizziness and three reported feeling sleepy. Exposure to 280 ppm for 2 h or 600 ppm for 10 min resulted in a loss of motor coordination in groups of four subjects. Exposure to 1,060 ppm tetrachloroethylene was so irritating to the eyes and upper respiratory tract of four subjects that the maximal exposure period tolerated was 1 to 2 min. Recovery from these effects occurred following cessation of exposure.

Although Rowe et al. (1952) reported that no adverse CNS effects were observed after exposure of subjects to ~100 ppm tetrachloroethylene for 1 h, Stewart et al. (1970) found that exposure of 11 subjects to a mean tetrachloroethylene concentration of 101 ppm for 7 h produced symptoms such as headache, dizziness, difficulty in speaking, and sleepiness. Of five objective tests of CNS performance, none showed any abnormality except the Romberg test of balance, which was abnormal in three of the five subjects exposed for 7 h/day for 5 consecutive days. Only one exposure level was used in this study, and no control subjects were included (Stewart et al. 1970).

Stewart et al. (1977) evaluated 12 subjects in a complicated study design utilizing alternating exposures to 0, 25, or 100 ppm tetrachloroethylene for 5.5 h per exposure session. Subjects were also given diazepam and/or alcohol in combination with an exercise regime. Testing was generally 5 days/week for 11 weeks. On most weeks, two of the exposure days were to 0 ppm tetrachloroethylene. Subjects were evaluated using the following tests: Romberg balance test, Flanagan coordination test (a measure of hand-eye coordination), eye saccade velocity measurement, the Lorr-McNair mood scale, a rotary pursuit test, and EEG evaluations. Stewart et al. (1977) concluded that based on the results of all the behavioral tests, tetrachloroethylene at concentrations of up to 100 ppm had no consistent effects on test performance.

Hake and Stewart (1972) reported the same study results as Stewart et al. (1977). In addition, they reported results from an additional tetrachloroethylene study in which resting subjects were exposed to 0, 20, 100, and 150 ppm tetrachloroethylene for 7.5 h (4 males). Females were exposed to 0 or 100 ppm for 7.5 h, and other groups of subjects were exposed to 100 ppm for 1 or 3 h. Subjects were exposed 5 days/week. It appears that the male subjects were exposed sequentially to the different exposure concentrations with 5 days of exposure per concentration. Subjective evaluation of EEG scores suggested cortical depression in subjects exposed to 100 ppm. Visually evoked responses and equilibrium tests were normal. Behavioral tests were done only on male subjects. Math skills, time discrimination, inspection, and reaction times were normal. Flanagan coordination scores, as measured by the Flanagan coordination test, were significantly decreased "on at least 1 day" during weeks of 100- and 150-ppm exposure.

The previously described studies suggest that the threshold for CNS effects in humans resulting from acute duration exposures is in the concentration range of 100 to 200 ppm. It should be noted that the discrepancy in the results of the Stewart et al. (1970, 1977) studies [i.e., inconsistent effects on the Romberg test at the same exposure concentration (100 ppm)], the differences in exposure duration between the Stewart et al. (1970, 1977) and Rowe et al. (1952) studies, and the reversible, inconsistent and/or subjective nature of the effects preclude a more precise determination of a threshold.

Reports of accidental exposures also indicate that CNS effects such as dizziness, confusion, headache, and nausea result from low-level tetrachloroethylene exposure (EPA 1985a). Higher level, short-term exposures intensified these symptoms and produced unconsciousness and death. Other case studies indicate that extended exposure to tetrachloroethylene results in many of the temporary CNS symptoms produced by short-term exposures and those more continuous or of longer duration (EPA 1985a). Long-term exposed subjects are also reported to experience effects such as short-term memory defects, ataxia, irritability, disorientation, and sleep disturbances (EPA 1985a). Although case studies document the CNS effects of tetrachloroethylene exposure, the data are poor or nonexistent, and the exposures are potentially confounded by exposure to other chemicals.

Inhalation, animal. Open-field behavior (ambulation) was elevated in groups of 10 male rats exposed to 200 ppm (1,356 mg/m^3) tetrachloroethylene of unspecified purity for 6 h/day for 4 days (Savolainen et al. 1977). Observations showed that ambulation was significantly increased 1 h after the last exposure. This effect was not observed 17 h after the last exposure. Biochemical analyses of the brains were conducted following additional 2- to 6-h exposures to tetrachloroethylene on the fifth day. Effects included reduced RNA content and increased nonspecific cholinesterase content.

Groups of eight Mongolian gerbils (four of each sex) were exposed to 0 or 60 ppm and 0 or 320 ppm tetrachloroethylene in separate experiments continuously for 3 months, followed by a 4-month exposure-free period (Rosengren et al. 1986). Concentrations of S-100 (an astroglial protein), DNA, and protein were determined in different regions of the brain. Effects at 320 ppm included increased concentrations of S-100 in the hippocampus, cerebral occipital cortex, and cerebellar areas; decreased concentrations of S-100 in the frontal cerebral cortex; decreased DNA content in the frontal cerebral cortex, sensory-motor cerebral cortex, and posterior cerebellar hemispheres; increased protein concentration per wet weight in the sensory-motor cerebral cortex; and decreased wet weight of the frontal cerebral cortex. Decreased DNA concentration in the frontal cerebral cortex was the only effect associated with exposure to 60 ppm tetrachloroethylene.

Brain amino acid and glutathione concentrations were determined in groups of six Mongolian gerbils (three of each sex) that were exposed to 0 or 120 ppm tetrachloroethylene continuously for 12 months (Briving et al. 1986). Treatment-related effects included decreased taurine content in the hippocampus and posterior part of the cerebellar vermis and increased glutamine content in the hippocampus. Uptake of glutamate and gamma-aminobutyric acid (GABA) into the cerebellum and hippocampus was unaffected.

Continuous exposure of six male Mongolian gerbils to 120 ppm tetrachloroethylene for 12 months also caused an alteration in the fatty acid composition of a phospholipid (phosphatidylethanolamine) in the cerebral cortex and hippocampus (Kyrklund et al. 1984).

Partial daily (4 to 7 h/day) inhalation exposure of rats to higher concentrations of tetrachloroethylene (>1,000 ppm) produced effects such as ataxia and somnolence, progressing to anesthesia after several days (Carpenter 1937, Rowe et al. 1952, Goldberg et al. 1964). The effects typically diminished with repeated exposures, suggesting development of an adaptational response.

Whether the biochemical changes occurring in certain areas of the brain after tetrachloroethylene inhalation can be used as an index of neuronal damage, or merely represent adaptive effects, is unclear. However, according to Rosengren et al. (1986), proliferation of astroglial cells and of S-100 protein are indicative of brain damage. Also, Briving et al. (1986) noted that increased glutamine levels are usually observed during and after degeneration of neurons.

Oral, human. Few studies were identified in the available literature in which neurotoxic effects were reported after ingesting tetrachloroethylene. The effects seen in humans after ingesting tetrachloroethylene appear to parallel those seen after inhalation.

A 6-year-old child who ingested 12 to 16 g of tetrachloroethylene was conscious upon admission to a hospital 1 h after ingestion, but his level of consciousness deteriorated to somnolence and subsequently coma (Koppel et al. 1985). Other symptoms included drowsiness, vertigo, agitation, and hallucinations.

The oral administration of tetrachloroethylene as a treatment for hookworm infestation in humans was common at one time; however, newer therapeutic agents have since replaced tetrachloroethylene for this use. Narcotic effects, inebriation, and exhilaration, but not death, were observed in patients receiving 2.8- to 4-mL (~4.2- to 6-g) doses of tetrachloroethylene orally as an antihelminthic (Kendrick 1929, Lambert 1933, Wright et al. 1937, Sandground 1941, Haerer and Udelman 1964).

Oral, animal. No studies were identified in the available literature that addressed the neurotoxicity of tetrachloroethylene to animals after oral exposure.

Dermal. No studies on the neurotoxic effects of dermally applied tetrachloroethylene in humans or animals were identified in the available literature.

General discussion. The symptomatology of acute inhalation exposure to high levels of tetrachloroethylene is well documented in humans and includes eye and upper respiratory irritation, headache, dizziness, and drowsiness. It is important to note that human and animal data are not inconsistent in indicating a threshold region for CNS effects. Human data (Stewart et al. 1970, 1977; Rowe et al. 1952) suggest that the threshold may be in the concentration range of 100 to 200 ppm, and studies with gerbils, using more sensitive indices (brain biochemistry), indicate exposure-related alterations at concentrations as low as 60 ppm for continuous exposure (Rosengren et al. 1986).

The mechanism of tetrachloroethylene neurotoxicity has not been elucidated. One cause for the CNS-depressant effects of tetrachloroethylene may be the incorporation of this lipophilic compound into brain membranes, thereby altering parameters such as neural conduction velocity. Kyrklund et al. (1984) have shown that tetrachloroethylene alters the fatty acid pattern of brain phospholipids. Furthermore, long-term exposure to lipophilic solvents has been shown to lead to increasing tolerance over time with regard to membrane altering and neurobehavioral effects. This phenomenon may explain the tolerance to ataxia and stupor demonstrated in rats after prolonged exposure to tetrachloroethylene (Rowe et al. 1952, Goldberg et al. 1964).

Damage to the CNS has been associated with hypertrophy and/or proliferation of astroglial cells. Rosengren et al. (1986) reported an increase in brain-level S-100, an astroglial protein, after a 3-month continuous exposure of guinea pigs to 320 ppm tetrachloroethylene. In a recent abstract, Haglid et al. (1985) reported that tetrachloroethylene (dose and route unstated) administered to rats resulted in "astroglial reactions" that could be interpreted as irreversible astroglial hypertrophy and/or proliferation. Briving et al. (1986) showed a tetrachloroethylene-induced increase in free glutamine in the hippocampus. Increased free glutamate may act as a biomarker for astroglial hypertrophy and/or hyperplasia since glutamine synthetase is located exclusively in astrocytes. Although evidence of astroglial hypertrophy does not fully elucidate a mechanism for tetrachloroethylene-induced neurotoxicity, it does provide histological and biochemical evidence to support the theory that neuronal damage occurs after tetrachloroethylene exposure.

Briving et al. (1986) also found a significant decrease in brain taurine content in gerbils exposed to 120 ppm tetrachloroethylene continuously for 12 months. Taurine is known to be a nonspecific membrane stabilizer; therefore, a reduction in the content of this amino acid may lead to alterations in nerve impulse transmission and could be responsible for tetrachloroethylene-induced neurotoxic effects.

Rosengren et al. (1986) indicated that the decreased DNA content observed in the brain of gerbils exposed continuously to tetrachloroethylene concentrations as low as 60 ppm represented a decreased cell density, most likely from the loss of cells. It was suggested that this may represent the development of brain atrophy.

4.3.2.2 Hepatic effects

Inhalation, human. Tetrachloroethylene has been known since the early 1960s to be hepatotoxic to humans. A number of reports of liver damage after inhalation of tetrachloroethylene in acute or chronic exposure situations have been documented (Hake and Stewart 1977, Klassen and Plaa 1967, Levine et al. 1981, Saland 1967); however, these reports consist entirely of case studies of accidental exposures, and reliable quantitative exposure information is not available. Hepatotoxic effects attributed to tetrachloroethylene exposure include cirrhosis of the liver, toxic hepatitis, liver cell necrosis, hepatomegaly, and altered liver function indices [serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), bilirubin, and alkaline phosphatase] (EPA 1985a).

Inhalation, animal. Moderate fatty degeneration of the liver was observed in mice 1 day after a single 4-h exposure to 200 ppm tetrachloroethylene, but not 3 days after exposure (Kylin et al. 1963). In mice that received single 4-h exposures to 400, 800, or 1,600 ppm tetrachloroethylene, moderate to massive fatty degeneration was observed 1 and 3 days after exposure. Fatty degeneration of the liver also occurred in groups of 20 mice exposed to 200 ppm tetrachloroethylene 4 h/day, 6 days/week for 1, 2, 4, or 8 weeks (Kylin et al. 1965).

Liver weight, liver pathology, and plasma butyrylcholinesterase (BuChe) activity were evaluated in groups of 30 NMRI mice of each sex exposed to 0, 9, 37, 75, or 150 ppm tetrachloroethylene continuously for 30 days (Kjellstrand et al. 1984). Treatment-related effects included abnormal gross pathological appearance at ≥9 ppm, significantly increased liver weight at ≥9 ppm, and significantly increased BuChe activity at ≥37 ppm. Gross pathological alterations included enlargement and yellowish color. Histological examination revealed enlargement and vacuolization of hepatocytes from all areas of the liver, but normal trabecular arrangement. Although pathological alterations were observed at the 9-ppm exposure concentration, they were most pronounced above 75 ppm. Increased liver weight and serum BuChe activity also occurred in mice exposed continuously to 150 ppm tetrachloroethylene for 4, 8, or 14 days, and to those exposed intermittently at a TWA concentration of 150 ppm for 30 days. Liver weights were still increased (10%) 120 days following 30 days of continuous exposure to 150 ppm. It should be noted that the significance of increased serum BuChe activity in this study is unclear for two reasons: (1) there was wide variability in BuChe activity in the controls and (2) serum BuChe can be modulated by nonhepatic factors (Kjellstrand et al. 1984).

Tetrachloroethylene-induced histological alterations have been observed in the livers of rodents in other intermediate-duration inhalation studies (Carpenter 1937, Rowe et al. 1952, NTP 1986). These studies have not identified effects at concentrations <100 ppm, but none of the exposures were continuous and only one used mice.

Preliminary 13-week studies were conducted by NTP (1986) in which mice and rats were exposed to 100 to 1,600 ppm tetrachloroethylene 6 h/day 5 days/week. No adverse pathological effects occurred in either species at 100 ppm. In mice, mitotic alteration in the liver occurred at ≥200 ppm, and minimal-to-mild hepatic leukocytic infiltration, centrilobular necrosis, and bile stasis occurred at 400 to 1,600 ppm. Minimal-to-mild hepatic congestion occurred in rats at 200 to 800 ppm.

Carpenter (1937) exposed rats to tetrachloroethylene at average vapor concentration levels of 0, 70, 230, or 470 ppm for 8 h/day, 5 days/week for 7 months. There was no evidence of pathological changes in the livers of rats exposed to 70 ppm. Reduced hepatic glycogen storage was observed following exposure to 230 ppm and a 20-day recovery period, and congested livers with cloudy swelling, without necrosis or fatty degeneration, were observed after exposure to 470 ppm and a 46-day recovery period.

Rowe et al. (1952) exposed rats, rabbits, guinea pigs, and monkeys to tetrachloroethylene vapors at levels of 100 to 400 ppm, 7 h/day, 5 days/week for ~6 months. No histopathological findings were seen at any exposure level among treated rats, rabbits, or monkeys. Guinea pigs, however, were more susceptible to tetrachloroethylene, with adverse effects occurring at all exposure levels. Female guinea pigs exposed to 100 ppm tetrachloroethylene had increased liver weights with no histopathology, whereas both sexes of guinea pigs exposed to 200 ppm had increased liver weights with some fatty degeneration, a slight increase in hepatic lipid content, and the presence of several small hepatic fat vacuoles. Guinea pigs exposed to 400 ppm tetrachloroethylene had more pronounced liver changes than at the 200-ppm exposure level, including cirrhosis, increased liver weight, increased hepatic neutral fat and esterified cholesterol, and moderate hepatic central fatty degeneration.

In an NTP (1986) carcinogenicity bioassay, groups of 50 F344/N rats were exposed to 0, 200, or 400 ppm tetrachloroethylene, and groups of 50 B6C3F1 mice of each sex were exposed to 0, 100, or 200 ppm tetrachloroethylene for 6 h/day, 5 days/week for 103 weeks (NTP 1986). Treatment-related nonneoplastic hepatic effects, including degeneration and necrosis, occurred in mice exposed to 200 ppm. It should be noted that increased incidences of hepatocellular neoplasms occurred in mice at both 200- and 400-ppm concentrations (See Sect. 4.3.6.1).

Rampy et al. (1978) exposed Sprague-Dawley rats to 300 or 600 ppm tetrachloroethylene vapor for 6 h/day, 5 days/week for 12 months. The animals were then allowed to live until 31 months of age. Tetrachloroethylene was found not to be tumorigenic in this study. Furthermore, no treatment-related hepatic effects were noticed. However, it should be noted that 12 months of exposure is a relatively short period for assessing tumorigenic effects, which could have been evident if the exposure had been longer.

Oral, human. Clinical signs indicative of liver damage that occurs after acute tetrachloroethylene ingestion in humans include elevated SGOT and SGPT levels, hepatomegaly, and fatty degeneration of the liver cells (Koppel et al. 1985). However, these findings were not observed, on admission to the hospital, in a 6-year-old boy who ingested 12 to 16 g of tetrachloroethylene, possibly because these signs are often transient and generally appear at a later stage (Koppel et al. 1985). Also, the rapid therapeutic intervention that increased the elimination of tetrachloroethylene by hyperventilation may have contributed to the diminished clinical signs.

Oral, animal. Groups of male Swiss-Cox mice were administered tetrachloroethylene (>99% pure) in corn oil by gavage at doses of 0, 20, 100, 200, 500, 1,000, 1,500, or 2,000 mg/kg 5 days/week for 6 weeks (Buben and O'Flaherty 1985). Group sizes were 26 (0 ppm), 13 to 19 (100 to 1,000 ppm), and 6 (1,500 and 2,000 ppm). Four parameters of hepatotoxicity were evaluated at all dose levels: relative liver weight, triglycerides, glucose-6-phosphatase (G6P) activity, and SGPT activity. There were no effects on these parameters at 20 mg/kg. Liver weight and triglycerides were significantly increased at ≥100 mg/kg; G6P was significantly decreased and SGPT was significantly increased at ≥500 mg/kg. The effects were nearly all dose-dependent, although liver triglycerides peaked and SGPT levels reached a plateau at 1,000 mg/kg. Histological examination of livers from mice in the 200- and 1,000-mg/kg dose groups showed severe degenerative changes with evidence of karyorrhexis (nuclear disintegration); centrilobular necrosis occurred in some of the livers at 1,000 mg/kg. Plots of the hepatotoxicity parameters against total urinary metabolites were linear in all cases, suggesting that the hepatotoxicity is directly related to the degree of tetrachloroethylene metabolism.

Hayes et al. (1986) administered estimated doses of 0, 14, 400, or 1,400 mg/kg/day tetrachloroethylene via drinking water to groups of 20 Sprague-Dawley rats of each sex for 90 consecutive days. Relative liver weight was significantly increased in both sexes at 1,400 mg/kg/day. Serum 5'-nucleotidase, an enzyme indicator of possible liver damage, was significantly increased at 400 and 1,400 mg/kg/day in the males and at 1,400 mg/kg/day in the females. There were no treatment-related effects on other serum indicators of hepatotoxicity (e.g., SGOT, SGPT, LDH, and bilirubin), and gross pathological effects were not observed.

Dermal. No studies on the hepatic effects of dermally applied tetrachloroethylene in humans or experimental animals were identified in the available literature.

General discussion. Tetrachloroethylene is regarded as a hepatotoxin in humans and animals by the inhalation and oral routes of exposure. The types of tetrachloroethylene-induced hepatic effects are reasonably well documented, but the exposures or doses producing these effects are less adequately characterized. For humans, reports of hepatotoxicity consist entirely of case studies of accidental exposures in which reliable quantitative exposure information was not available. In most cases, hepatic effects in humans have been reported as transient in nature. In animals, interpretation of hepatotoxicity is complicated by differences in exposure schedule, sensitivity of end points, sensitivity of species, and a paucity of chronic-duration exposures. The animal data do indicate that mice are a particularly sensitive species. Recent data indicate that short-term exposure to tetrachloroethylene by gavage or by inhalation induces peroxisome proliferation in mouse liver, which has been suggested to account for the carcinogenic response in mouse liver (Goldworthy and Popp 1987, Odum et al. 1988). The data also suggest that similar hepatic effects may be produced by intermittent and continuous exposures when the TWA dose is the same, and that tetrachloroethylene-induced hepatic effects of intermediate-duration exposures are not totally reversible.

4.3.2.3 Renal effects

Inhalation, human. Symptoms of renal dysfunction, including diminished excretion of urine, uremia, elevated serum creatine, proteinuria, and hematuria, have been associated with accidental exposure to tetrachloroethylene vapor (Hake and Stewart 1977, Larsen et al. 1977). The exposures were not quantified, and a cause-effect relationship with tetrachloroethylene exposure cannot be inferred because other factors may have been responsible for the effects (EPA 1985a). However, Franchini et al. (1983) reported that workers in dry-cleaning workshops exposed for an average of 14 years to an estimated time-weighted average of 10 ppm of tetrachloroethylene had increased urinary levels of lysozyme and β-glucuronidase; these effects were considered to be weak. In another report, Lauwerys et al. (1983) did not observe any adverse effects on the kidney or on the central nervous system or liver of dry-cleaning workers exposed to 6 ppm of tetrachloroethylene for 6 years.

Inhalation, animal. Carpenter (1937) exposed albino rats to tetrachloroethylene at average vapor concentration levels of 0, 70, 230, or 470 ppm for 8 h/day, 5 days/week for 7 months. There was no evidence of pathological changes in the kidneys of rats exposed to 70 ppm. Renal congestion was observed following exposure to 230 ppm and a 20-day recovery period, and increased renal secretion with cloudy swelling and desquammation in the kidneys (details not specified) was observed after exposure to 470 ppm and a 46-day recovery period.

The results of other intermediate-duration inhalation studies with rats (Rowe et al. 1952, NTP 1986) are inconsistent with the results of Carpenter (1937). In the study by Rowe et al. (1952), abnormal renal function or histopathological findings were not observed in rats, rabbits, guinea pigs, or monkeys exposed to tetrachloroethylene vapor concentrations of 0, 100, 200, or 400 ppm for 7 h/day, 5 days/week for ~6 months. An additional group of guinea pigs that received 14 exposures to 400 ppm in 18 days, however, showed increased kidney weights but no histological alterations (Rowe et al. 1952). Guinea pigs that received eighteen 7-h exposures to 2,500 ppm tetrachloroethylene in 20 days had increased kidney weights, with slight-to-moderate cloudy swelling of the tubular epithelium.

Rats and mice were exposed to 0, 100, 200, 400, 800, or 1,600 ppm tetrachloroethylene vapor for 6 h/day, 5 days/week for 13 weeks in a preliminary study for the NTP (1986) carcinogenicity bioassay. Kidney histological alterations were not observed in the rats. Karyomegaly (nuclear enlargement) of the renal tubule epithelial cells occurred in mice exposed to 1,600 ppm, but survival was reduced at this concentration.

In the NTP (1986) bioassay, groups of 50 F344/N rats of each sex were exposed to 0, 200, or 400 ppm tetrachloroethylene, and groups of 50 B6C3F1 mice were exposed to 0, 100, or 200 ppm tetrachloroethylene for 6 h/day, 5 days/week for 103 weeks. Renal tubular cell karyomegaly occurred in both species at all exposure concentrations at incidences that were dose-related. This alteration was accompanied by low incidences of renal tubular cell hyperplasia in male rats; however, no significant increases in hyaline droplet formation were noted. Decreased survival occurred in low- and high-dose male mice after weeks 74 to 78 and in high-dose female mice after week 90.

Oral, human. Acute renal failure and glomerulonephritis were noted as possible late-stage consequences of acute oral tetrachloroethylene ingestion in humans (Koppel et al. 1985). Specific reports of renal effects in humans resulting from ingestion of tetrachloroethylene were not found in the available literature.

Oral, animal. Tetrachloroethylene doses of 0, 15, 400, or 1,400 mg/kg/day were administered via drinking water to groups of 20 Sprague-Dawley rats of each sex for 90 consecutive days (Hayes et al. 1986). Relative kidney weights were significantly increased in the males at 400 mg/kg/day and in both sexes at 1,400 mg/kg/day. There were no treatment-related effects on urinalysis indices or gross kidney pathology. Unpublished data were used in the evaluation of this study.

Groups of 50 Osborne-Mendel rats and B6C3F1 mice of each sex were exposed to tetrachloroethylene in corn oil by gavage 5 days/week for 78 weeks, followed by observation periods of 32 weeks (rats) and 12 weeks (mice) in a carcinogenicity bioassay (NCI 1977). TWA doses for the study were 450 and 550 mg/kg/day for male mice, 300 and 400 mg/kg/day for female mice, 471 and 941 mg/kg/day for male rats, and 474 and 949 mg/kg/day for female rats; untreated and vehicle control groups included 20 animals of each sex for each species. Toxic nephropathy occurred at all dose levels in both sexes of rats and mice, but increased mortality also occurred at these doses. The nephropathy in both species was characterized by degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium.

Goldworthy et al. (1987) showed that short-term administration of tetrachloroethylene to male F/344 rats in the diet produces an increase in protein droplet accumulation and cell proliferation in the P2 segment of the kidney. This effect, not seen in female rats, was correlated with an increased presence of α-2μ globulin, a male-rat specific protein, in the proximal convoluted epithelial cells.

Dermal. No studies reporting renal effects of dermally applied tetrachloroethylene in humans or experimental animals were identified in the available literature.

General discussion. Renal effects resulting from inhalation or oral exposure to tetrachloroethylene are documented in rodents but not in humans. However, tetrachloroethylene should be regarded as a probable nephrotoxin in humans, because nonproliferative kidney lesions are characteristic effects of various halogenated aliphatic hydrocarbons (particularly chlorinated ethanes and ethylenes) in animals and humans (Kluwe et al. 1984, NTP 1986). Kluwe et al. (1984) reviewed human case reports and case-control studies and showed that there is a positive statistical association between mixed organic solvent exposure and chronic kidney disease.

As indicated above, tetrachloroethylene induced protein droplet nephropathy in male rats, which is characterized by accumulation of α-2μ globulin in lysosomes, degeneration and necrosis of tubular cells, formation of granular casts, and regeneration of the tubular epithelium (Swenberg et al. 1988). Chemicals that are known to induce protein droplet bind to α-2μ globulin, yielding a complex that is more resistant to the proteolytic enzymes in the lysosomes, leading to the accumulation of the complex in the tubule cells. α-2μ Globulin has not been found in immature male rats, female rats, or humans (Alden 1986). If tetrachloroethylene induced nephropathy by the suggested mechanism, the absence of α-2μ globulin in humans raises the question of the relevance to humans of the tetrachloroethylene-induced kidney lesions in male rats. Humans synthesize other related low molecular weight proteins that may bind chemicals that cause α-2μ nephropathy in rats, but this does not necessarily indicate human risk.

4.3.2.4 Immunotoxicity

Inhalation, human. Pertinent data regarding the immunotoxicity of tetrachloroethylene in humans exposed by inhalation were not found in the available literature.

Inhalation, animal. Susceptibility to infection from inhaled *Streptococcus zooepidemicus* and pulmonary bactericidal activity from inhaled *Klebsiella pneumoniae* were evaluated in groups of 140 female CD-1 mice that were exposed to 0 or 25 ppm tetrachloroethylene or 0 or 50 ppm tetrachloroethylene (separate tests) for 3 h (Aranyi et al. 1986). Mortality over 14 days from the streptococcal aerosol challenge was significantly increased, and bactericidal activity to *K. pneumoniae* was significantly decreased in the 50-ppm treatment group when compared with its control group. Interpretation of the effects at 50 ppm is complicated by the results of the 25-ppm test in which the control mortality rate was higher than in any of the other treated or control groups in the study. In another test, exposure to 0 or 25 ppm tetrachloroethylene for 3 h/day for 5 days did not cause treatment-related effects on streptococcal-induced mortality or bactericidal activity.

Although the significance of the Aranyi et al. (1986) study is unclear because of the variability in control group mortality and despite the lack of evaluation of other immunotoxicological end points and other immunotoxicity studies, the results of this study suggest that inhalation of tetrachloroethylene may increase susceptibility to respiratory infection. The increased susceptibility may be related to a reduction in pulmonary bactericidal activity.

Tsulaya et al. (1977) exposed rats to tetrachloroethylene vapors and could not detect production of antibodies to tetrachloroethylene with the passive hemagglutination reaction.

4.3.2.5 Cardiotoxicity

Inhalation, human. Human data suggest an association between exposure to tetrachloroethylene and cardiotoxic effects. Hara et al. (1985) evaluated the cardiovascular status of 55 asymptomatic Japanese dry-cleaning workers selected to avoid a history of hypertension, diabetes mellitus, and heavy ethanol intake. The workers were divided into two categories, those indirectly exposed to organic solvents (presumably including tetrachloroethylene but not otherwise specified) and those directly exposed. Exposure levels were not quantified. A group of age- and sex-matched unexposed controls was also studied. Exposure to organic solvents appeared to have no effect on electrocardiography. Echocardiography revealed statistically significant increased ventricular wall thickness-to-radius ratio, decreased fractional shortening of the internal dimension of the left ventricle, and decreased mean velocity of circumferential fiber shortening at systole in exposed workers. The intensity of these effects increased in an exposure-related manner, with the greater intensity observed in the directly exposed group. The investigators stated, however, that there was no direct evidence of cause and effect. Furthermore, exposure may have been to a variety of organic solvents.

Abedin et al. (1980) reported the case of a 24-year-old male who experienced skipped heart beats, headache, and dizziness within 1 month after starting work in a dry-cleaning operation. Upon hospitalization after 7 months of employment, electrocardiograms revealed sinus rhythm and ventricular premature beats that gradually disappeared during hospitalization. Plasma tetrachloroethylene was measured at 0.15 ppm on the fifth day of hospitalization. The patient was discharged the next day, but returned in 2 weeks for outpatient evaluation with a recurrence of the previously reported symptoms. At that time, plasma tetrachloroethylene was measured at 3.8 ppm. The patient was reported to be asymptomatic 1 month after finding different employment.

Inhalation, animal. Reinhardt et al. (1973) investigated the ability of tetrachloroethylene to sensitize the hearts of male beagle dogs to epinephrine-induced cardiac arrhythmias, as evaluated by electrocardiography. Epinephrine (8 μg/kg) was intravenously infused before and after 10 min of exposure to tetrachloroethylene at 5,000 and 10,000 ppm. Exposed dogs showed signs of excitement and struggling (associated with stage II anesthesia), but exposure was not associated with a "marked" change in the electrocardiogram when epinephrine was infused. The investigators did not report effects on the electrocardiogram of dogs exposed to tetrachloroethylene without epinephrine.

Kobayashi et al. (1982) evaluated the effects of intravenously injected tetrachloroethylene on the cardiac sensitivity to the epinephrine challenge in anesthetized rabbits, cats, and dogs. Each animal (five rabbits, seven cats, and six dogs) was evaluated for EKG and blood pressure responses to epinephrine. Various doses of epinephrine were administered (0.25, 0.6, and 1 μg/kg for rabbits; 5, 10, 15, and 20 μg/kg for cats; and 2.5, 5, and 10 μg/kg for dogs). Twenty minutes following the base-line challenge, the same dose of epinephrine was administered, followed by intravenous injection of tetrachloroethylene (5 to 10 mg/kg in rabbits, 10 to 40 mg/kg in cats, and 5 to 20 mg/kg in dogs). The tetrachloroethylene was administered in 0.05% TWEEN 80. Following the dose of tetrachloroethylene, a second dose of epinephrine was administered. The authors concluded that in all three species, tetrachloroethylene produced ventricular arrhythmias and increased epinephrine-induced sensitivity to premature ventricular contractions, bigeminy, and tachycardia. Rabbits appeared to be the most sensitive, showing tachycardia at 5 mg/kg tetrachloroethylene and increased ventricular ectopic activity after exposure to 10 mg/kg tetrachloroethylene. Statistically significant increases in arrhythmias in response to tetrachloroethylene only occurred when the base-line heart rate was >100 beats/min. The authors also suggested that 20 to 40 mg/kg tetrachloroethylene administered to dogs produced direct myocardial depression. This conclusion was based on observations of significant depression in the rate of rise of left intraventricular pressure, with the absence of significant effects on arterial pressure. The authors also suggested that cardiac effects are not generally seen in humans as a result of limited pulmonary absorption.

Oral. Data were not found regarding the cardiotoxicity of tetrachloroethylene in orally exposed humans or animals.

Dermal. Data were not found regarding the cardiotoxicity of tetrachloroethylene in dermally exposed humans or animals.

General discussion. Despite the relatively large number of people occupationally exposed to tetrachloroethylene, there are few reported cases of tetrachloroethylene-associated cardiotoxicity. The case study presented by Abedin et al. (1980) suggests an association of tetrachloroethylene with effects on the heart, but the patient described may have been an unusually sensitive individual. These investigators hypothesized that exposure to tetrachloroethylene may sensitize the myocardium to endogenous epinephrine. In an experiment in dogs, however, inhalation exposure to high levels of tetrachloroethylene failed to sensitize the heart to epinephrine (Reinhardt et al. 1973). In contrast, intravenous administration of tetrachloroethylene enhanced myocardial sensitivity to an exogenous epinephrine challenge (Kobayashi et al. 1982).

4.3.2.6 Dermal/ocular effects

Morgan (1969) and Ling and Lindsay (1971) reported two cases in which humans accidentally exposed to tetrachloroethylene in dry-cleaning workshops developed severe erythema and blistering of the skin. In a study conducted by Wayne et al. (1960), vapors of tetrachloroethylene at 5 or 20 ppm, irradiated with nitrogen dioxide in order to simulate the atmospheric conditions of Los Angeles County, did not produce appreciable eye irritation in human volunteers.

4.3.3 Developmental Toxicity

4.3.3.1 Inhalation

Human. Information regarding the developmental effects of inhaled tetrachloroethylene in humans was not found in the available literature.

Animal. Schwetz et al. (1975) exposed 17 pregnant Sprague-Dawley rats and 17 pregnant Swiss-Webster mice to tetrachloroethylene by inhalation at concentrations of 0 or 300 ppm for 7 h/day on days 6 to 15 of gestation. The fetuses were examined for external, soft tissue, and skeletal anomalies on day 21 of gestation. Statistically significant effects in the treated rats included a reduction in maternal mean weight and an increase in fetal resorptions in 9 of 17 litters. Statistically significant effects in the treated mice included increased maternal mean relative liver weight, decreased mean fetal weight, increased incidences of subcutaneous edema, delayed ossification of skull bones, and split sternebrae. Teratogenicity or effects on other embryotoxic or fetotoxic indices were not reported in either species, and histological examinations of saggital sections of one whole fetus from each litter were unremarkable.

In an unpublished teratogenicity study reported by EPA (1985a), Sprague-Dawley rats were exposed to 0 or 300 ppm (2,034 mg/m^3) tetrachloroethylene for 7 h daily (Beliles et al. 1980). Additional information regarding experimental design is ambiguous: exposures were 5 days/week (schedule during gestation exposure not specified), 19 to 24 rats were examined (numbers exposed not specified), one-half of the rats were exposed for 3 weeks prior to mating, and all rats were exposed during gestation on days 0 to 18 or 6 to 18 (numbers exposed or examined in each group not specified). Concentrations in the exposure chamber either fluctuated or were higher than intended, since measurements taken 15 min before the end of exposure showed 568 ppm. Treatment-related effects reportedly included maternal ataxia, loss of balance and death during pregestational exposure, decreased maternal weight gain, increased maternal absolute (not relative) liver and kidney weights, and unspecified fetal skeletal ossification anomalies. Teratogenic or additional embryotoxic effects were not observed.

In an associated study, Hardin et al. (1981) exposed Sprague-Dawley rats to 500 ppm tetrachloroethylene for 6 to 7 h/day on gestational days 1 to 19. It is stated that the target number of litters per group was 30; however, the actual numbers were not given. Tetrachloroethylene was scored negative for maternal toxicity, fetal toxicity, and teratogenicity (actual data not reported). The brevity of result and protocol reporting makes this study difficult to interpret.

In the same report, results of exposure of rabbits to 500 ppm tetrachloroethylene for 6 to 7 h/day on days 1 to 24 of gestation are also discussed. The target number of litters per group was given as 20 (actual numbers not reported). Again, tetrachloroethylene was scored negative for maternal toxicity, fetal toxicity, and teratogenicity.

In a behavioral teratology study, groups of 13 to 21 Sprague-Dawley rats were exposed for 7 h/day to 0 or 100 ppm tetrachloroethylene on days 14 to 20 of gestation, to 0 or 900 ppm tetrachloroethylene on days 14 to 20, and to 0 or 900 ppm tetrachloroethylene on days 7 to 13 (Nelson et al. 1980). Seven behavioral tests were used to evaluate effects at several stages of development (postnatal days 4 to 46); one male and one female from each litter were used for each test. Neurochemical analyses and histological examinations of whole brains (except cerebellum) were conducted on pups at 0 or 21 days of age. Effects were not associated with 100-ppm treatment. Effects occurred in rats exposed to 900 ppm, including reduced maternal feed consumption and weight gain, without liver or kidney histological alterations, and decreased performance of pups exposed on gestation days 7 to 13 during the tests of neuromuscular ability (ascent and rotorod) on certain days. Offspring from dams exposed on days 14 to 20 also performed poorly on the ascent test on one test day, but later in development performance, they were superior to controls; activity also increased in the open-field test. Results of the neurochemical analyses showed, for 21-day-old offspring, decreases in dopamine in those exposed on gestation days 14 to 20 and decreases in acetylcholine in those exposed on days 7 to 13 or 14 to 20.

Additional developmental testing of rats exposed to high concentrations of tetrachloroethylene has been conducted. In an unpublished study reported by EPA (1985a), Long-Evans hooded rats were exposed to 0 or 1,000 ppm (6,780 mg/m^3) tetrachloroethylene for 6 h/day, 5 days/week for 2 weeks before mating through gestation day 20 or on days 0 through 20 of gestation (Tepe et al. 1982, Manson et al. 1982). Treatment-related effects included increased maternal liver weight, reduced fetal body weight, and increased unspecified skeletal and soft-tissue anomalies indicative of embryotoxicity. Neurobehavioral testing of offspring at 10 to 170 days of age was unremarkable. In a pilot study to the Nelson et al. (1980) behavioral teratology study, exposure of Sprague-Dawley rats to 900 ppm tetrachloroethylene (schedule not specified) on days 7 to 13 or 14 to 20 of gestation did not produce fetal external or skeletal malformations.

4.3.3.2 Oral

Human. Information regarding the developmental effects of ingested tetrachloroethylene in humans was not found in the available literature.

Animal. Information regarding the developmental effects of orally administered tetrachloroethylene in animals was not found in the available literature.

4.3.3.3 Dermal

Human. Information regarding the developmental effects of dermally applied tetrachloroethylene in humans was not found in the available literature.

Animal. Information regarding the developmental effects on dermally applied tetrachloroethylene in animals was not found in the available literature.

4.3.3.4 Discussion

Developmental studies have been conducted in rats and mice (one study) exposed to tetrachloroethylene by inhalation. The results of these studies indicate that tetrachloroethylene is fetotoxic but not teratogenic at concentrations that are also maternally toxic. Fetotoxicity was usually expressed by decreased fetal weight and delayed skeletal ossification. These effects have been associated with exposures ≥300 ppm, and NOAELs have not been reported. Gestational exposure to higher concentrations of tetrachloroethylene (900 ppm) was associated with minor behavioral and neurochemical alterations in some rat offspring, but this may also reflect maternal nutritional deprivation rather than a direct effect of tetrachloroethylene (Nelson et al. 1980).

Ghantous et al. (1986) noted a high concentration of the tetrachloroethylene metabolite TCA in the amniotic fluid of mice following maternal inhalation exposure to tetrachloroethylene. This finding, the authors note, suggests that TCA may be transported to the fetus via the transplacental route through the fetal membranes and amniotic fluid. Such a pathway indicates that the fetus may be exposed to a large extent by swallowing the amniotic TCA or absorbing it through the skin. Because TCA also appeared in the fetal urinary bladder, the authors noted that it is likely that TCA recirculates several times before leaving the fetoplacental compartment. This process may contribute to long-term retention in the fetus.

The mechanism by which tetrachloroethylene produces embryotoxicity is not known; however, in view of the high concentration of TCA found in the fetal tissues (Ghantous et al. 1986), it seems likely that the observed fetotoxicity might equally well be due to metabolites as to the unmetabolized tetrachloroethylene. This assumption is strengthened by the fact that a low concentration of radioactivity from administered radiolabeled tetrachloroethylene was found in the fetal brain, and high activity appeared in other organs.

Tetrachloroethylene should be studied more extensively as a potential transplacental neurotoxicant, since the results of the Nelson et al. (1980) study suggest the possibility of delayed neurobehavioral effects. The rapid absorption, minimal metabolism transformation, and slow excretion of tetrachloroethylene are unfavorable pharmacokinetic characteristics with regard to in utero exposure.

4.3.4 Reproductive Toxicity

4.3.4.1 Inhalation

Human. Information regarding the reproductive effects of inhaled tetrachloroethylene in humans was not found in the available literature.

Animal. Carpenter (1937) did not detect any adverse effects on reproductive performance among rats exposed to 70, 230, or 470 ppm tetrachloroethylene for 8 h/day, 5 days/week for 28 weeks, as judged by the number of pregnancies, number of litters conceived, and number of offspring per litter.

Male rats were exposed to 100 or 500 ppm tetrachloroethylene for 7 h/day for 5 consecutive days in unpublished dominant-lethal and sperm-morphology assays (Beliles et al. 1980). Sperm morphology was also examined in identically treated mice in the same study. The only treatment-related effect was an increased frequency of abnormal sperm (19.7% vs 6.0% in controls) in mice exposed to 500 ppm tetrachloroethylene during the fourth week after exposure (the spermatocyte stage). (See Sect. 4.3.5.2).

4.3.4.2 Oral

Human. Information regarding the reproductive effects of ingested tetrachloroethylene in humans was not found in the available literature.

Animal. Information regarding the reproductive effects of orally administered tetrachloroethylene in animals was not found in the available literature.

4.3.4.3 Dermal

Human. Information regarding the reproductive effects of dermally applied tetrachloroethylene in humans was not found in the available literature.

Animal. Information regarding the reproductive effects of dermally applied tetrachloroethylene in animals was not found in the available literature.

4.3.4.4 Discussion

Limited information is available regarding the reproductive effects of inhaled tetrachloroethylene in animals. The finding of abnormal sperm in mice exposed to 500 ppm tetrachloroethylene is an indication of chemical effects on the sperm; however, definitive evidence that tetrachloroethylene or its metabolites or impurities reached germinal tissue and damaged DNA is not provided. Although the results of the dominant-lethal assay with rats were negative, it should be recognized that this is a relatively insensitive assay that is generally thought to measure gross chromosome damage (EPA 1985a).

4.3.5 Genotoxicity

4.3.5.1 Human

The lymphocytes from ten people occupationally exposed to tetrachloroethylene concentrations between 10 and 220 ppm for 3 months to 18 years were examined for chromosome aberrations and sister chromatid exchange (Ikeda et al. 1980). There was no increase in these parameters compared with controls. Tetrachloroethylene-induced DNA damage (i.e., lesions), as measured by unscheduled DNA synthesis, was studied in human fibroblast cells by Beliles et al. (1980). The results of this study were equivocal, however, because of a positive response at the lowest test concentration and negative responses at two higher concentrations. Also, the positive control chemicals [*N*-methyl-*N'*-nitro-*N*-nitrosoguanidine and benzo(a)pyrene] used in this study elicited only weak responses.

4.3.5.2 Nonhuman

A large number of studies of the in-vitro genotoxicity of tetrachloroethylene have been performed using prokaryotic, eukaryotic, and mammalian cells. The results are summarized in Table 4.1. Tetrachloroethylene itself has not been clearly shown to be a mutagen. Certain commercial and technical preparations have induced positive responses in the Ames bacterial test, a yeast recombinogenic assay, a host-mediated assay using *Salmonella*, and DNA repair assays. Responses were weak and required high concentrations of the chemical. No clear dose-response relationship could be established in these studies. Impurities and stabilizers could have contributed to the responses. The potential mutagenicity of stabilizers and contaminants is relevant in

Table 4.1. Genotoxicity of tetrachloroethylene in vitro

End point	Species (test system)	Result		References
		No activation	Activation	
Prokaryotic system				
Gene mutation	*Salmonella typhimurium*	–	–	Bartsch et al. 1979, SRI 1983, Margard 1978, NTP 1983, Haworth et al. 1983, Williams and Shimada 1983, Cerna and Kypenova 1977, Kringstad et al. 1981
	Escherichia coli	–	–	Greim et al. 1975, Henschler 1977
Lower eukaryotic system				
Gene mutation	*Saccharomyces cerevisiae*	–	–	Callen et al. 1980, Bronzetti et al. 1983
Recombination	*S. cerevisiae*	Mixed	–	Bronzetti et al. 1983, Callen et al. 1980
Mammalian cells				
Cell transformation	RaLV/Fisher rat embryo cells	+	NR[a]	Price et al. 1978
	BALB/C3T3 mouse cells	–	NR	Tu et al. 1985
	L5178Y/$TK^{+/-}$ mouse lymphoma cells	–	–	NTP 1986
DNA damage	Rat and mouse hepatocyte	–	NR	Costa and Ivanetich 1984, Williams and Shimada 1983, Williams 1983
	Human fibroblast cells	Mixed	Mixed	Beliles et al. 1980
Sister chromatid exchange	Chinese hamster ovary cells	–	–	NTP 1986

[a] Not reported.

terms of assessing the effects associated with exposure to commercial tetrachloroethylene products. Highly purified tetrachloroethylene has only been evaluated in the *Ames/Salmonella* test, where negative results were obtained. Furthermore mutagenic responses could have been obscured by lack of appropriate controls, sample sizes that were too small, or inadequate exposure conditions. In addition, no studies have been reported regarding the ability of tetrachloroethylene to cause chromosome nondisjunction, which would result in aneuploidy, a significant genotoxic effect. An epoxide of tetrachloroethylene was found to be mutagenic in bacterial studies (Kline et al. 1982), leading to the testing of the parent compound in the presence of several types of metabolic activation systems. The results were largely negative or weakly positive, suggesting that inadequate information exists to warrant a provisional classification of tetrachloroethylene either as nonmutagenic or mutagenic.

Studies of the in vivo genotoxicity of tetrachloroethylene are summarized in Table 4.2. A variety of assays have been used to study in vivo tetrachloroethylene genotoxicity, and, for the most part, the results of these assays have been negative.

4.3.6 Carcinogenicity

4.3.6.1 Inhalation

The only investigation of dry-cleaning workers with no known exposure to petroleum solvents was a subcohort of 615 workers from the Brown and Kaplan (1985) retrospective mortality study. Excess risk for cancer at any site was not identified in the subcohort. In the entire cohort, which was comprised of 1,690 workers (including workers who had potential occupational exposure to petroleum solvents), there were significant excesses of mortality from kidney and bladder cancer (8 cases vs 2.7 expected; SMR = 296) and cancer of the cervix (10 observed vs 5.1 expected; SMR = 196).

Epidemiological studies of dry-cleaning and laundry workers have determined significant excesses in mortality due to cancers of the lung, cervix, kidney, skin and/or colon (Blair et al. 1979, Kaplan 1980, Katz and Jowett 1981, Duh and Asal 1984, Brown and Kaplan 1985). Although these studies suggest a possible association between chronic occupational exposure to tetrachloroethylene and increased cancer risk, the evidence must be regarded as inconclusive, because workers were exposed to petroleum solvents and other dry-cleaning agents as well as tetrachloroethylene, because other confounding factors such as smoking and low socioeconomic status were not considered in the analyses, because the numbers of site-specific deaths were low, and because attempts were not made to distinguish between laundry and dry-cleaning workers. It must be mentioned that in an epidemiological study conducted by Smith et al. (1985), no increase in the incidence of bladder cancer was found among laundry workers and dry-cleaners as compared to control subjects.

Table 4.2. Genotoxicity of tetrachloroethylene *in vivo*

End point	Species/test system	Results	References
Sister chromatid exchange	Human lymphocytes/sister chromatid exchange	–	Ikeda et al. 1980
DNA damage	Mouse/induction of single strand breaks in DNA	+	Walles 1986
DNA binding or alkylation	Mouse/tetrachloroethylene binding to or alkylation of liver DNA	–	Schumann et al. 1980
Germ cell chromosome damage	Rat, mouse/genetic damage in germinal system	–	Beliles et al. 1980
Mutation in germ cells	Rat, mouse/altered sperm morphology	Mixed	Beliles et al. 1980
Host-mediated assays	Mouse/*Salmonella typhimurium* in animal host	+	Cerna and Kypenova 1977
Gene mutation	*Drosophila melanogaster*/ sex-linked recessive lethal mutation	–	Beliles et al. 1985, Valencia et al. 1985
Chromosomal aberration	Rat bone marrow cells/ chromosomal aberrations	–	Rampy et al. 1978 Beliles et al. 1980, Cerna and Kypenova 1977
	Human lymphocytes/ chromosomal aberrations		Ikeda et al. 1980
Gene mutation	*Drosophila melanogaster*/ sex-linked recessive lethal mutation	–	NTP 1986

Animal. NTP (1986) conducted inhalation carcinogenicity studies in which groups of 50 F344/N rats of each sex were exposed to 0, 200, or 400 ppm tetrachloroethylene, and groups of 50 B6C3F1 mice of each sex were exposed to 0, 100, or 200 ppm tetrachloroethylene. Exposures were 6 h/day, 5 days/week for 103 weeks. Statistically significant increased incidences of mononuclear cell leukemia occurred in the treated male rats (28/50 in controls, 37/50 at low dose, 37/50 at high dose) and female rats (18/50, 30/50, 29/50); the increases in the males were marginally significant ($P = 0.046$ in both dose groups). Low incidences of renal tubular cell adenomas or adenocarcinomas (1/49, 3/49, 4/50) occurred in male rats; however, these tumors are considered uncommon in untreated male rats. Although the incidence of these tumors was not statistically significant, there was a significant trend. In mice, there were significantly increased incidences of hepatocellular adenomas (11/49, 8/49, 18/50) and hepatocellular carcinomas (7/49, 25/49, 26/50) in males and hepatocellular carcinomas (1/48, 13/50, 36/50) in the females.

Rampy et al. (1978) exposed groups of 96 male and 96 female Sprague-Dawley rats to tetrachloroethylene vapors at levels of 2 or 4 g/m^3 (300 or 600 ppm, respectively), 6 h/day, 5 days/week for 12 months. The animals were kept for observation for an additional 18 months. There was no statistically significant difference in any tumor incidence between treated and control animals.

The EPA (1986) calculated inhalation unit risk for tetrachloroethylene based on the metabolized dose estimated directly from the empirical data and on the metabolized dose derived from the PB-PK model. These approaches led to the calculation of very similar values for unit risk. It must be noted that some of the parameters used in the PB-PK model were estimated from the same data that were used in the empirical approach. Therefore, in this particular case, the PB-PK model does not necessarily add reliability.

4.3.6.2 Oral

Human. Information regarding the carcinogenicity of ingested tetrachloroethylene in humans was not found in the available literature.

Animal. Groups of 50 Osborne-Mendel rats and 50 B6C3F1 mice of each sex were exposed to tetrachloroethylene in corn oil by gavage 5 days/week for 78 weeks, followed by observation periods of 32 weeks (rats) and 12 weeks (mice) in an NCI (1977) carcinogenicity bioassay. TWA doses were 471 and 941 mg/kg/day for male rats, 474 and 949 mg/kg/day for female rats, 450 and 550 mg/kg/day for male mice, and 300 and 400 mg/kg/day for female mice. Groups of 20 untreated and vehicle-treated rats and mice of each sex served as controls. No increases in tumor incidences were observed for the treated rats. Statistically significant increases in hepatocellular carcinomas occurred in the treated mice of both sexes. Incidences in the untreated control, vehicle control, low-dose, and high-dose groups were 2/17, 2/20, 32/49, and 27/48 in male mice, and 2/20, 0/20, 19/48, and 19/48 in female mice. Metastases occurred in one untreated control male, in three low-dose males, and in one low-dose female and one high-dose female. As indicated in the National Research Council, Drinking Water and Health

Document (1980), the findings of the NCI (1977) study must be interpreted with caution because of "the limitation of the experimental design (e.g., massive doses of tetrachloroethylene, large volumes of oil vehicle, marked nephrotoxicity and diminished lifespan)."

4.3.6.3 Dermal

Human. Information regarding the dermal carcinogenicity of tetrachloroethylene in humans was not found in the available literature.

Animal. Tetrachloroethylene was not tumorigenic to female Ha:ICR mice when applied to the skin at doses of 18 or 54 mg per mouse in an acetone vehicle three times weekly for life (440 to 594 days) (Van Duuren et al. 1979). No treatment-related papillomas or carcinomas of the skin or tumors at distant sites were produced. In the same report, tetrachloroethylene showed slight but not significant tumor-initiating activity in the mouse skin two-stage carcinogenesis test system when phorbol myristate acetate (PMA) was used as the promotor.

4.3.6.4 Discussion

Epidemiological studies of dry-cleaning workers suggest a possible association between chronic tetrachloroethylene exposure and increased cancer risk, but the likelihood of concomitant exposure to petroleum solvents and the effects of other confounding factors and methodological limitations make the results of these studies inconclusive. The carcinogenicity of tetrachloroethylene is documented in animals. In chronic inhalation studies (NTP 1986), tetrachloroethylene exposure was associated with a higher-than-expected incidence of mononuclear cell leukemia in rats and hepatocellular adenomas and carcinomas in mice. In chronic oral studies (NCI 1977), tetrachloroethylene produced hepatocellular carcinomas in mice, but not in rats. It has been hypothesized that differences in the hepatocarcinogenicity of tetrachloroethylene between rats and mice are possibly due to species differences in peroxisome proliferation resulting from higher trichloroacetic acid blood levels in mice. Trichloroacetic acid results from the biotransformation of tetrachloroethylene and has been shown to induce liver peroxisome proliferation in mice but not in rats (Goldworthy and Popp 1987). These findings, together with supporting evidence showing the mutagenicity of tetrachloroethylene epoxide (a reactive metabolite), constitute a "sufficient" level of evidence for the carcinogenicity of tetrachloroethylene in animals using the EPA (1986) weight-of-evidence criteria. It must be noted, however, that the strains of rats and mice used in these studies have a high spontaneous incidence of tumors and the mechanism of tumor formation in these animals may not be operative in humans. Overall, considering the inconclusive evidence for carcinogenicity in humans, EPA (1986) has recommended a Group B2 weight-of-evidence classification. EPA's Science Advisory Board has commented that a continuum between Group C and B2 may be appropriate. IARC (1987) has considered the data and given a classification of 2B. As of January 1989, EPA has not taken a final position on the weight of evidence.

4.4 INTERACTIONS WITH OTHER CHEMICALS

If, as postulated, metabolism of tetrachloroethylene through an epoxide intermediate is a prerequisite for tetrachloroethylene-induced toxicity (Buben and O'Flaherty 1985), then compounds that stimulate or induce tetrachloroethylene metabolism should increase the toxicity associated with exposure to this chemical. Results of experiments that have investigated possible enhancement of tetrachloroethylene-induced toxicity by increasing tetrachloroethylene metabolism have been mixed. Pretreatment of rats with ethanol (Cornish and Adefuin 1966) and phenobarbital (Cornish et al. 1973, Moslen et al. 1977) failed to enhance tetrachloroethylene toxicity. Pretreatment with polychlorinated biphenyls (PCBs), on the other hand, increases urinary excretion of tetrachloroethylene metabolites in rats and enhances tetrachloroethylene-induced hepatotoxicity (Moslen et al. 1977). This potentiation of tetrachloroethylene-induced toxicity by pretreatment with PCBs has been postulated to be due to the increased metabolism of tetrachloroethylene to its corresponding epoxide, which, in turn, is due to induction of microsomal enzymes by PCBs.

High doses of intravenously administered tetrachloroethylene have been found to sensitize the myocardium to the presence of exogenous epinephrine (Kobayashi et al. 1982). However, Reinhardt et al. (1973) did not observe sensitization to epinephrine in beagle dogs exposed to vapors of tetrachloroethylene.

5. MANUFACTURE, IMPORT, USE, AND DISPOSAL

5.1 OVERVIEW

Tetrachloroethylene is a commercially important chlorinated hydrocarbon solvent and chemical intermediate. It has been widely used as a dry-cleaning and textile-processing solvent and for vapor degreasing in metal-cleaning operations. Currently, four U.S. manufacturers (operating six production facilities) produce about 0.5 billion lb of tetrachloroethylene annually. Imported quantities of tetrachloroethylene are significantly larger than exported quantities.

5.2 PRODUCTION

The following companies have been cited as current U.S. manufacturers of tetrachloroethylene (SRI 1987): Dow Chemical (Pittsburg, California, and Plaquemine, Louisiana); Occidental Petroleum Corporation (Deer Park, Texas); PPG Industries (Lake Charles, Louisiana); and Vulcan Materials Company (Geismar, Louisiana, and Wichita, Kansas). The approximate annual production capacity of these manufacturers is 720 million lb (SRI 1987). DuPont closed a tetrachloroethylene production facility in Corpus Christie, Texas, in 1986 (CMR 1986). In addition to the manufacturers, numerous other companies function as distributors of this chemical, supplying the many small end users who lack storage facilities (Chemical Products Synopsis 1985).

United States production volumes of tetrachloroethylene in recent years have been reported as follows (Chemical and Engineering News 1987; USITC 1981, 1982, 1983, 1984, 1985, 1986):

Year	Production (millions of pounds)
1986	414
1985	678
1984	573
1983	547
1982	585
1981	691
1980	765

The future production market for tetrachloroethylene has been projected at either zero growth or a long-term gradual decline (CMR 1986, Chemical Products Synopsis 1985).

Tetrachloroethylene, like other chlorinated hydrocarbon solvents, can be made by the acetylene process, by direct chlorination of certain hydrocarbons, or by oxychlorination. The acetylene method, involving reaction of feedstock acetylene with chlorine, was the preferred method for many years, but according to Keil (1985), it is no longer widely used because of the high cost of acetylene. Trichloroethylene (TCE) is produced as an intermediate in this reaction sequence to manufacture tetrachloroethylene. Keil (1985), Considine (1974), and Chemical Products Synopsis (1985) all describe a simultaneous chlorination and pyrolysis process in which chlorine is reacted with a hydrocarbon such as methane, ethane, propane, or propylene, or a chlorinated hydrocarbon derivative, to yield a crude product from which marketable-grade tetrachloroethylene is derived following distillation and purification. This route, which is both feasible and more economical, is currently used to produce tetrachloroethylene. Keil (1985) states that "~40% of current United States production is based on ethane and propane." Hydrogen chloride is produced as a by-product of this reaction. The third method, oxychlorination of ethylene via ethylene dichloride, is widely used to coproduce TCE and tetrachloroethylene without any net production of hydrogen chloride (Keil 1985, Chemical Products Synopsis 1985).

Tetrachloroethylene is produced in purified, technical, USP, and spectrophotometric grades. It is also produced as fluorocarbon grade for use in the production of CFC-113. The various grades satisfy dry-cleaning, technical, industrial, and vapor-degreasing requirements, respectively. Inhibitors are added to extend solvent life and protect equipment and materials (Chemical Products Synopsis 1985). Tetrachloroethylene, which is thus stabilized and not easily hydrolyzed, is transported in tanks and drums.

5.3 IMPORT

Importation of tetrachloroethylene has increased sharply since 1980 because of the strength of the dollar abroad (Chemical Products Synopsis 1985). United States imports of tetrachloroethylene in 1983 and 1984 were 61 and 142 million lb, respectively, with the major countries exporting to the United States being Canada, West Germany, Spain, and Romania (U.S. Department of Commerce 1984, 1985).

5.4 USE

Tetrachloroethylene is commercially important primarily as a chlorinated hydrocarbon solvent and as a chemical intermediate. The current end-use pattern for tetrachloroethylene has been estimated to be 53% for dry cleaning and textile processing, 28% as a chemical intermediate (mostly for fluorocarbon F-113), 10% for industrial metal cleaning, 5% for exports, and 4% for other uses (CMR 1986).

In textile processing, tetrachloroethylene functions as a scouring solvent, removing oils from fabrics after knitting and weaving operations, and as a carrier solvent for fabric finishes and water repellants and for sizing and desizing (Chemical Products Synopsis 1985). Tetrachloroethylene has the ability to dissolve fats, greases, waxes, and oils without harming natural or man-made fibers. Nevertheless, because of such factors as the growing popularity of wash and wear fabrics, improved efficiency of equipment, and increased chemical recycling, the demand for tetrachloroethylene as a dry-cleaning solvent has declined steadily in the last few years. At the same time, a sharp increase has occurred in the use of tetrachloroethylene as a chemical intermediate for the manufacture of two-carbon chlorofluorocarbons, especially F-113 (trichlorotriflouroethane), as well as other chemicals (Chemical Products Synopsis 1985, IARC 1979).

Vapor and liquid degreasing and metal cleaning constitute the third major use of tetrachloroethylene. This chemical dissolves certain inorganic compounds and many organic compounds, as well as high-melting pitches and waxes; thus, it is especially applicable for cleaning and drying contaminated metal parts and other fabricated materials, and, according to Verschueren (1983), it is used to remove soot from industrial boilers.

Numerous miscellaneous uses account for the remaining demand for tetrachloroethylene. Additional general solvent uses include carrier applications for rubber coatings, solvent soaps, printing inks, adhesives and glues, sealants, polishes, lubricants, and silicones (Chemical Products Synopsis 1985, Mitchell 1980). Tetrachloroethylene is also miscible with other common solvents and is an ingredient in blended solvents (Considine 1974); it forms as many as 60 binary azeotropic mixtures (Keil 1985). Other reported uses are as follows: nonflammable, recyclable dielectric fluid for power transformers; heat transfer medium; extractant in the pharmaceutical industry; pesticide intermediate; and intermediate for the production of trichloroacetic acid (Hawley 1981, Verschueren 1983, U.S. Department of Health and Human Services/U.S. Department of Labor 1978, Considine 1974). Windholz (1983) has reported tetrachloroethylene's therapeutic use as an antihelminthic in the treatment of hookworm and some trematode infestations. However, the Consumer Product Safety Commission (CPSC) has discouraged other reported consumer uses such as inclusion as an ingredient in aerosols and formulations of shoe polish (IARC 1979).

5.5 DISPOSAL

In recent years, the chemical industry has responded to heightened environmental and ecological concerns with efforts to improve recovery and recycling of tetrachloroethylene. Historical methods of disposal have included absorption in vermiculite, dry sand, earth, or a similar material for burial in a secured sanitary landfill (U.S. Department of Health and Human Services/U.S. Department of Labor 1978) and incineration after mixing with another combustible fuel (Sittig 1985). In the latter method, care should be taken to carry out combustion to completion and, thereby, prevent the formation of phosgene. An acid scrubber must be used to remove the haloacids produced.

Recent federal regulations prohibit the land disposal of various chlorinated solvent materials that may contain tetrachloroethylene. Federal, state, and local authorities should be consulted for updated regulations concerning tetrachloroethylene disposal.

6. ENVIRONMENTAL FATE

6.1 OVERVIEW

Most of the tetrachloroethylene used in the United States is released into the atmosphere by evaporative losses. The dry-cleaning industry is the major source of these evaporative losses. The dominant tetrachloroethylene degradation process in the atmosphere is the result of reaction with hydroxyl radicals, which have an estimated half-life of ~96 days in typical air. This relatively long half-life permits long-range global atmospheric transport of tetrachloroethylene, thereby causing exposures at remote regions far removed from emission sources. The detection of tetrachloroethylene in rainwater indicates that physical removal from the atmosphere by washout can occur. Tetrachloroethylene present in surface waters or on soil surfaces will predominantly volatilize into the atmosphere. Tetrachloroethylene is moderately to highly mobile in soil and susceptible to significant leaching. In subsurface regions where volatilization cannot occur, tetrachloroethylene is only slowly degraded and may be relatively persistent. Reviews pertaining to the environmental fate of tetrachloroethylene are available (Callahan et al. 1979, Gilbert et al. 1982, EPA 1985a, HSDB 1987).

6.2 RELEASES TO THE ENVIRONMENT

It has been estimated that 80 to 85% of the tetrachloroethylene used annually in the United States is released to the environment, particularly to the atmosphere (Gilbert et al. 1982, IARC 1979). A major portion of the atmospheric releases occurs from evaporative losses in the dry-cleaning industry (Gilbert et al. 1982). Other atmospheric emissions occur from metal-degreasing uses, production of fluorocarbons and other chemicals, textile industry uses, and miscellaneous solvent-associated applications (Gilbert et al. 1982, Weant and McCormick 1984). Environmental releases of tetrachloroethylene also occur at sites of its manufacture and at sites of production of other chlorohydrocarbons (such as ethylene dichloride and methylene chloride) in which tetrachloroethylene is formed as a by-product (Weant and McCormick et al. 1984). Tetrachloroethylene emissions to the atmosphere also occur at landfill sites containing the chemical (EPA 1985a). Tetrachloroethylene has been detected in stack effluents from municipal waste incinerators (James et al. 1984).

Releases of tetrachloroethylene to water appear to be minor in comparison to atmospheric releases. A variety of the tetrachloroethylene-use industries (such as metal degreasing and dry cleaning) release tetrachloroethylene water-associated wastes to sewer and waste treatment facilities (Gilbert et al. 1982, Weant and McCormick 1984). It appears that aeration processes at waste treatment facilities strip much of the tetrachloroethylene from the water and release it into the atmosphere as a result of the high volatility of this chemical (Lurker et al. 1982). Tetrachloroethylene is emitted to groundwater from landfill leaching (DeWalle and Chian 1981, Sabel and Clark 1984, Reinhard et al. 1984, Kosson et al. 1985).

Many of the processes in which tetrachloroethylene is used as a solvent involve recycling the compound by various methods (Gilbert et al. 1982). These recycling methods produce tetrachloroethylene-containing sludges and dirty filters that have been landfilled in the past.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Laboratory studies have demonstrated that tetrachloroethylene volatilizes rapidly from water (Smith et al. 1980, Roberts and Dandliker 1983, Okouchi 1986, Dilling 1977, Dilling et al. 1975, Matter-Mueller et al. 1981, Chiou et al. 1980). Although volatilization is rapid, actual volatilization rates are dependent on temperature, water movement and depth, associated air movement, and other factors. The volatilization half-life of tetrachloroethylene from a rapidly moving, shallow river (1 m deep, flowing 1 m/s with a wind velocity of 3 m/s) is ~4.2 h (Lyman et al. 1982). Using the experimentally measured tetrachloroethylene-oxygen reaeration ratio of 0.52 (Smith et al. 1980) and average reaeration rates for typical environmental bodies of water (Mabey et al. 1981), tetrachloroethylene volatilization half-lives for these typical bodies of water can be estimated as follows: pond, 7 days; river, 1.4 days; and lake, 5.6 days. Measured volatilization half-lives in a mesocosm, which simulated Narraganset Bay, Rhode Island, during winter, spring, and summer, ranged from 11 to 25 days (Wakeham et al. 1983). Measurement of tetrachloroethylene levels in Lake Zurich, Switzerland, has indicated that volatilization is the dominant elimination process in surface waters (Schwarzenbach et al. 1979).

Experimentally measured soil sorption coefficients (K_{oc}) for tetrachloroethylene range from 137 to 363 (Chiou et al. 1979, Friesel et al. 1984, Kenaga 1980, Schwarzenbach and Westall 1981, Seip et al. 1986). These K_{oc} values are indicative of medium-to-high soil mobility (Swann et al. 1983). The significant movement of tetrachloroethylene in soil has been confirmed by bank-infiltration systems in Switzerland and the Netherlands, where tetrachloroethylene has been observed to leach rapidly into groundwater (Giger et al. 1983, Piet et al. 1981). A considerable number of monitoring studies have detected tetrachloroethylene in groundwater (see Sect. 7, Potential for Human Exposure), which is further evidence of its leachability. This also indicates that tetrachloroethylene will not partition significantly from the water column to sediment in natural bodies of water.

Tetrachloroethylene has been detected in a number of rainwaters collected in the United States (see Sect. 7, Potential for Human Exposure). This may indicate that physical removal by means of wet deposition is an important environmental fate process with respect to tetrachloroethylene. The relatively high vapor pressure of tetrachloroethylene indicates that it is expected to exist entirely in the vapor phase in the ambient atmosphere and not partition to atmospheric particulates. Significant evaporation from dry surfaces can also be predicted from the high vapor pressure.

Experimentally measured bioconcentration factors (BCF) for tetrachloroethylene in fish have been found to range from 39 to 49 (Barrows et al. 1980, Neely et al. 1974, Veith et al. 1980, Kenaga 1980). Two Japanese studies have also found tetrachloroethylene to have low bioaccumulation potential (Sasaki 1978, Kawasaki 1980). Monitoring tetrachloroethylene concentrations in seawater and associated aquatic organisms is in agreement with the experimental BCF data (Pearson and McConnell 1975, Dickson and Riley 1976).

6.3.2 Transformation and Degradation

The dominant transformation process for tetrachloroethylene in the atmosphere is expected to be the result of reaction with photochemically produced hydroxyl radicals (Singh et al. 1982). Using the recommended rate constant for this reaction (1.67×10^{-13} cm^3/(molecule-s) and a typical atmospheric hydroxyl radical concentration of 5×10^5 molecules/cm^3 (Atkinson 1985), the half-life is ~96 days. The degradation products of this reaction include phosgene and chloroacetylchlorides (Singh et al. 1975). Reaction of tetrachloroethylene with ozone in the atmosphere is too slow to be environmentally important (Atkinson and Carter 1984). The predicted degradation half-lives of tetrachloroethylene in the atmosphere indicate that long-range global transport is likely (Class and Ballschmiter 1986). Indeed, monitoring data have demonstrated that tetrachloroethylene is present in the atmosphere worldwide and at locations far removed from anthropogenic emission sources (see Sect. 7, Potential for Human Exposure).

In natural water and soil systems, biodegradation and hydrolysis may be the most important tetrachloroethylene transformation processes, although neither process appears to occur rapidly in the environment. Various biodegradation screening tests and laboratory studies have found tetrachloroethylene to be resistant or only biodegraded slowly (Bouwer et al. 1981, Bouwer and McCarty 1982, Mudder and Musterman 1982, Sasaki 1978, Wakeham et al. 1983, Wilson et al. 1983a). Other screening studies have noted more rapid biodegradation; however, appropriate inocula and microbial adaptations are necessary (Tabak et al. 1981; Parsons et al. 1984, 1985). The hydrolysis half-life of tetrachloroethylene in water at room temperature is ~9 months (Dilling et al. 1975).

Since neither biodegradation nor hydrolysis occurs at a rapid rate, most tetrachloroethylene present in surface waters can be expected to volatilize into the atmosphere. Volatilization will not, however, be a viable process for much of the tetrachloroethylene transported into groundwaters by leaching. There is evidence that slow biodegradation of tetrachloroethylene occurs under anaerobic conditions with acclimated microorganisms (Bouwer and McCarty 1984, Wilson et al. 1983b), suggesting that a slow degradation process (of biodegradation and hydrolysis) may occur in subsurface environmental regions. In regions where volatilization is not viable, tetrachloroethylene may be relatively persistent.

7. POTENTIAL FOR HUMAN EXPOSURE

7.1 OVERVIEW

The general population of the United States is exposed continually to tetrachloroethylene levels in the breathable air. In general, atmospheric levels are highest in areas of concentrated industry and population and decrease with movement to rural and remote regions. Inhalation exposure to tetrachloroethylene is highest in workers in the dry-cleaning industry. The general population can also be exposed to this chemical by contact with and/or consumption of contaminated water supplies and by consumption of contaminated foodstuffs. Based on available federal and state surveys, between 7 and 25% of the water supply sources in the United States may have some tetrachloroethylene contamination. Tetrachloroethylene has been found in at least 330 of the 1,177 National Priorities List (NPL) hazardous waste sites (VIEW 1989).

7.2 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

7.2.1 Air

A compilation of available U.S ambient air monitoring data for tetrachloroethylene prior to 1981 has been published (Brodzinsky and Singh 1982). This compilation, which includes >2,500 monitoring points, has determined mean tetrachloroethylene concentrations of 160 ppt in rural and remote areas, 790 ppt in urban and suburban areas, and 1,300 ppt in areas near emission sources. A similar compilation (EPA 1985a), with inclusion of data from throughout the world, has estimated the average background level of tetrachloroethylene to be 40 ppt in the northern hemisphere and 12 ppt in the southern hemisphere; the average urban level of tetrachloroethylene was found to be 800 ppt.

Recent ambient air monitoring studies in the United States have found tetrachloroethylene concentrations of 58 to 305 ppt in Portland, Oregon, in 1984 (Ligocki et al. 1985), 570 to 680 ppt in Philadelphia in 1983-84 (Sullivan et al. 1985), 240 to 590 ppt in three New Jersey cities during the summer of 1981 and the winter of 1982 (Harkov et al. 1984), and 292 to 590 ppt in seven cities (Houston, St. Louis, Denver, Riverside, Staten Island, Pittsburg, Chicago) in 1980-81 (Singh et al. 1982). Average levels of tetrachloroethylene detected in air in the Arctic between 1981 and 1983 are 75 to 81 ppt (Khalil and Rasmussen 1983, Hov et al. 1984).

Some of the highest outdoor air levels of tetrachloroethylene reported are associated with waste disposal sites, where maximum concentrations of 58,000 ppt have been found (EPA 1985a). Levels in excess of 7,000 ppt were detected in air monitoring at seven waste sites in New Jersey (Harkov et al. 1985).

Several comprehensive studies of humans have detected tetrachloroethylene in personal air (expired air) and have attempted to correlate the levels in personal air with those in water and ambient air (Wallace 1986; Wallace et al. 1985, 1986a; Krotoszynski et al. 1979).

7.2.2 Water

Compilations of tetrachloroethylene water monitoring data for drinking water, groundwater, and surface waters are available (HSDB 1987, EPA 1985a). The concentration of tetrachloroethylene in open oceans may be an indication of the environmental background levels in water. Average concentrations of 0.12 to 0.5 ppt have been detected in the North Atlantic (Pearson and McConnell 1975, Murray and Riley 1975), and levels <1 ppt were monitored in open waters of the Gulf of Mexico (Sauer 1981).

Tetrachloroethylene has been detected in many drinking waters throughout the United States. Median concentrations of 0.3 and 3.0 ppb were found in water from 180 U.S. cities using surface water supplies and 36 cities using groundwater supplies, respectively, with roughly 25% of all samples positive (Coniglio et al. 1980). The EPA Groundwater Supply Survey of 945 water supplies nationwide, using groundwater sources, found tetrachloroethylene in 75 waters; the median level of positive samples was ~0.75 ppb, with a maximum level of 69 ppb (Westrick et al. 1984). Tetrachloroethylene concentrations of 0.01 to 0.2 ppb were detected in drinking water from six cities (Cincinnati, Miami, Grand Forks, Lawrence, New York, Tucson) (Keith et al. 1976). Drinking water from wells in New York, New Jersey, and Connecticut have been found to contain tetrachloroethylene levels of 717 to 1,500 ppb, although these elevated levels were in areas of significant pollution (Burmaster 1982). Levels of 0.38 to 2.9 ppb were detected in tap water from homes near the Love Canal (Barkley et al. 1980).

A summary of U.S. groundwater analyses from both federal and state studies has found that tetrachloroethylene was detected in 14 to 26% of all samples analyzed (Dyksen and Hess 1982). Tetrachloroethylene was detected in 179 of 421 groundwaters from New Jersey, with a maximum concentration of 90 ppb (Page 1981). Tetrachloroethylene has been detected (at maximum levels of 590 ppb) in groundwater leachates from various landfill sites nationwide (DeWalle and Chian 1981, Sabel and Clark 1984, Reinhard et al. 1984, Kosson et al. 1985).

An analysis of the EPA STORET Data Base found that tetrachloroethylene was detected in 38% of 9,323 surface water reporting stations nationwide (Staples et al. 1985). An analysis of 1,140 samples from the Ohio River found a similar percentage of positive detections, with most detections <1 ppb (Ohio River Valley Sanitation Commission 1980). Tetrachloroethylene was found at levels >1 ppb at 77 sites and >10 ppb at one site during monitoring of 204 sites at 14 heavily industrialized river basins in the United States (HSDB 1987). Tetrachloroethylene was detected in 154 of 174 surface waters from New Jersey, with a maximum concentration of 4.5 ppb (Page 1981). Levels of 0.003 to 0.08 ppb were found in the Niagara River and Lake Ontario between 1978 and 1981 (Strachan and Edwards 1984).

7.2.3 Soil

Tetrachloroethylene has been qualitatively detected in the soil/sediment matrix of the Love Canal waste site near Niagara Falls (Hauser and Bromberg 1982). Sediments from Liverpool Bay near Great Britain were found to contain concentrations ranging from 0.03 to 6 ppm, with most detections at the lower limit (Pearson and McConnell 1975). Sediment levels of 0.3 ppb tetrachloroethylene have been identified in Lake Pontchartrain in Louisiana (Ferrario et al. 1985). An analysis of the EPA STORET Data Base found that tetrachloroethylene had been positively detected in 5% of 359 sediment observation stations, with median levels <5 ng/g (Staples et al. 1985).

7.2.4 Other

7.2.4.1 Foodstuffs

Tetrachloroethylene has been detected in dairy produce (milk, cheese, and butter at 0.3 to 13 μg/kg), meat (English beef at 0.9 to 1.0 μg/kg), oils and fats at 0.01 to 7 μg/kg, beverages (canned fruit drink, instant coffee, and tea at 2 to 3 μg/kg), fruits and vegetables (potatoes, apples, pears, and tomatoes at 0.7 to 2 μg/kg), and in fresh bread at 1 μg/kg (McConnell et al. 1975). Tetrachloroethylene concentrations of 0.4, 2, 2.2, 2.5, 1.6, and 3.6 ppb were detected in plant tap water, Chinese-style sauce, quince jelly, crab apple jelly, grape jelly, and chocolate sauce, respectively, obtained from a food processor in Pennsylvania (Entz and Hollifield 1982).

7.2.4.2 Precipitation

Rainwater collected in Portland, Oregon, in 1984 was found to contain tetrachloroethylene levels of 0.82 to 9.2 ng/L (Ligocki et al. 1985). A March 1982 rainwater sample from Los Angeles, California, contained 21 ng/L (Kawamura and Kaplan 1983). Tetrachloroethylene concentrations of 5.7 and 1.4 to 2.3 ng/L were detected in LaJolla, California, rainwater and in central-southern California snow, respectively (Su and Goldberg 1976). Levels up to 150 ng/L were found in rainwater in industrial cities in England (Pearson and McConnell 1975).

7.2.4.3 Fish

Concentrations of tetrachloroethylene (dry weight basis) detected in fish from the Irish Sea (eel, cod, coalfish, dogfish, bib) ranged from below detection limits to 43 ng/g, which was only 2 to 25 times greater than levels found in seawater (Dickson and Riley 1976). Levels of 0.3 to 43 ng/g (wet weight) were found in 15 species of fish collected off the coast of Great Britain (Pearson and McConnell 1975). Tetrachloroethylene was identified in a small number of fish in the Rhine River at concentrations generally between 0.025 and 0.1 mg/kg (Binnemann et al. 1983).

7.3 OCCUPATIONAL EXPOSURES

The National Institute for Occupational Safety and Health (NIOSH) has estimated that nearly 500,000 U.S. workers are at risk of exposure to tetrachloroethylene at over 20,000 dry-cleaning establishments and at a large number of other industries manufacturing or using the chemical (NIOSH 1978). Time-weighted-average (TWA) (8-h) exposures to tetrachloroethylene in air in the dry-cleaning industry have been reported to be as high as 178 ppm (HSDB 1987). An analysis of 67 dry-cleaning establishments in the United States determined mean TWA exposures ranging from 28.2 to 88.2 ppm, with the lower TWAs found at sites with better local exhaust systems (Materna 1985). A NIOSH survey of 44 dry-cleaning facilities found tetrachloroethylene TWA exposures to machine operators ranging from 4.0 to 149 ppm; the geometric mean tetrachloroethylene exposures to machine operators, pressers, seamstresses, and in front counter areas were 22, 3.3, 3.0, and 3.1 ppm, respectively (Ludwig et al. 1983). A study of the dry-cleaning industry in England found exposures similar to those in American studies (Shipman and Whim 1980).

7.4 POPULATIONS AT HIGH RISK

Various segments of the general population can be exposed to levels of tetrachloroethylene significantly above normal background concentrations. For example, indoor air in the vicinity of a dry-cleaning laundry has been found to have tetrachloroethylene levels as high as 32,000 ppt (EPA 1985a). Elevated levels of tetrachloroethylene in human breath appear to be related to tetrachloroethylene emissions from nearby factories or from chemical waste dumps (Monster and Smolders 1984).

Significantly elevated indoor air levels of tetrachloroethylene can occur in homes that use water supplies containing the volatilized chemical (Highland et al 1985, Andelman 1985). In one home, a running shower was found to elevate levels of tetrachloroethylene in bathroom air from <0.5 to 81 mg/m^3 within 17 min (Andelman 1985); this level is nearly one-third the American Conference of Governmental Industrial Hygienists (ACGIH) time-weighted threshold limit value (TLV) for workplace air.

Based on the EPA TEAM (Total Exposure Assessment Methodology) Study conducted in New Jersey, the following factors (in order of importance) were identified as areas with significantly increased tetrachloroethylene exposure by inhalation: employment (not otherwise specified), wood processing, visiting a dry cleaners, working at a textile plant, using pesticides, working at or being in a paint store, and being male (Wallace et al. 1986b).

8. ANALYTICAL METHODS

Several methods are available for analyzing tetrachloroethylene in different environmental and biological matrices. The choice of a particular method will depend on the nature of the sample matrix; the required precision, accuracy, and detection limit; and the cost and turnaround time of analysis. Preconcentrations of samples prior to quantification increase the detection limits of the method used. In air samples, the preconcentration usually is done by passing the air through a suitable adsorbent during sample collection. The dynamic headspace technique, commonly known as purge and trap, provides an excellent method for the preconcentration of tetrachloroethylene from water, food, soil, sediment, and biological matrices. The purge-and-trap method also provides a preliminary separation of tetrachloroethylene from other less volatile and nonvolatile components in the samples, thereby eliminating the need for extensive separation of the components by a gas chromatographic column prior to quantification. The best specificity and sensitivity for tetrachloroethylene quantification are obtained by both electron capture and electrolytic conductivity detectors in the halide detection mode, since these detectors are relatively insensitive to nonhalogenated species and very sensitive to halogenated species. Although mass spectrometry is less sensitive than electrolytic conductivity detection, it is often used as a confirmation method, since ion chromatograms of the fragment and parent ions provide an alternative confirmation in addition to gas chromatographic retention time. For details of the analytical methods, including the advantages and disadvantages, specificity, reproducibility, and sensitivity, refer to the references cited in Table 8.1.

8.1 ENVIRONMENTAL MEDIA

Analytical methods and detection limits for tetrachloroethylene in various environmental matrices are identified in Table 8.1. These methods are based primarily on gas chromatographic separation with subsequent quantification by various methods. Details of sample collection and preservation are provided in the references cited in Table 8.1.

8.2 BIOMEDICAL SAMPLES

Analytical methods and detection limits for tetrachloroethylene in various biomedical samples are identified in Table 8.1. Biological samples are commonly pretreated for analysis by a purge-and-trap method or a variation of that method. Details of the sample collection, preservation, pretreatment, and quantification methods are provided in references cited in Table 8.1. Since tetrachloroethylene is metabolized in the human body to trichloroethanol and trichloroacetic acid, the latter two compounds may be quantified in blood and urine as an indirect measure of tetrachloroethylene exposure (Monster et al. 1983). The rapid metabolism and excretion of trichloroethanol, however, requires the measurement of its concentration in urine within a few hours after exposure (Pekari and Aitio 1985). Because of the slower metabolism of tetrachloroethylene to trichloroacetic acid, the level of trichloroacetic acid in blood and urine can be measured several days after exposure (Monster et al. 1983, Pekari and Aitio 1985). It should be pointed out that the determination of trichloroethanol or trichloroacetic acid may not provide unambiguous proof of tetrachloroethylene exposure since these compounds are metabolites of trichloroethylene.

Table 8.1. Methods for analysis of tetrachloroethylene

Sample matrix	Sample preparation	Quantification method[a]	Detection limit	Accuracy/% recovery	References
Occupational air	Adsorption on charcoal, desorption with carbon disulfide	GC/FID (NIOSH method 8335 and 8336)	<20 ppm for 3-L sample	NR[b]	Peers 1985
Ambient air	Adsorption on charcoal, desorption with carbon disulfide/methanol	GC/ECD	0.1 ppb	70.2% (recovery from charcoal tubes)	Evans et al. 1979
	Adsorption on Tenax GC, thermal desorption	HRGC/MS	0.3 ppt	70–130%	Pellizzari and Bunch 1979, Krost et al. 1982
	Cryogenic trapping, thermal desorption	GC/ECD	0.2 ppt	85–115%	Singh et al. 1979, 1981; Rasmussen et al. 1977
Drinking water	Purge and trap in Tenax GC and thermal desorption	GC/HSD and GC/MS (EPA method 502.1 and 524.1)	0.3 ppb (MS) 0.03 ppb (HSD)	95% at 2 µg/L	EPA 1985b, APHA 1985
	Purge and trap in Tenax GC and thermal desorption	GC/Hall detector	0.05 ppb	62–69%	Wallace et al. 1986c,d
Water/wastewater	Purge and trap in Tenax GC and thermal desorption	GC/HSD and GC/MS (EPA method 601 and 624)	0.03 ppb (HSD) 4 ppb (MS)	94% (HSD) 101% (MS)	EPA 1982a
Water	Static headspace sampling	GC/FID; GC/ECD	32 ppb (FID) 0.01 ppb (ECD)	NR	Mieure 1980
	Purge at 40°C and trap in Tenax GC; thermal desorption	GC/FID; GC/Hall detector	1.0 ppb (FID) <0.1 ppb (Hall)	82% (Hall)	Otson and Williams 1982
Groundwater, liquid and solid matrices	Purge at 45°C and trap in Tenax GC; thermal desorption	GC/HSD (EPA method 8010)	0.03 ppb	94%	EPA 1982b
Food	Static headspace sampling from undigested or H_2SO_4-digested samples at 90°C	HRGC/ECD; GC/MS	0.5–13 ppb	51–84%	Entz et al. 1982

Table 8.1 (continued)

Sample matrix	Sample preparation	Quantification method	Detection limit	Accuracy/% recovery	References
Exhaled air	Collection of exhaled air in glass tubes and no sample pretreatment	GC/ECD	0.15 ppb	NR	Monster and Smolders 1984, Monster et al. 1983
	Exhaled air collected in Tedlar bag, concentrated by adsorption through Tenax GC and thermally desorbed	HRGC/MS	0.6 ppb	109–110%	Wallace et al. 1986c,d
Blood	Sample digested with H_2SO_4 at 60°C for 4 h; static headspace gas analyzed	GC/ECD	NR	NR	Monster et al. 1983
	Sample digested with H_2SO_4, dimethylsulfate at 60°C for 4 h; headspace gas analyzed	GC/ECD (for metabolite trichloroacetic acid)	30 ppb	NR	Monster et al. 1983, Monster and Boersma 1975
	Sample thermally decarboxylated and subjected to static headspace analysis	GC/ECD (for metabolite trichloroacetic acid)	2 ppb	101–107%	Ziglio et al. 1984
Urine	Sample thermally decarboxylated	Spectrophotometric (for metabolite trichloroacetic acid)	<0.8 ppm	93.5%	Pekari and Aitio 1985
Blood, plasma, or serum	Sample subjected to headspace analysis	GC/ECD	10 ppb	NR	Ramsey and Flannagan 1982
Tissue	Sample mixed with a proteolytic enzyme incubated at 65°C and headspace gas analyzed	GC/ECD	NR	NR	Ramsey and Flannagan 1982
Exhaled air	Sample collected in Teflon bag, preconcentrated by Tenax GC adsorption and thermal desorption	HRGC/FID	NR	NR	Krotoszynski et al. 1979
Mother's milk	Purging warm sample and trapping in Tenax GC and subsequent thermal desorption	HRGC/MS	Qualitative identification	NR	Pellizzari et al. 1982

[a] GC = Gas chromatography; FID = flame ionization detector; ECD = electron capture detector; HRGC = high resolution gas chromatography; MS = mass spectrometry; HSD = halide specific detector.

[b] Not reported.

9. REGULATORY AND ADVISORY STATUS

9.1 INTERNATIONAL

The World Health Organization has recommended a tentative drinking water guidance level of 10 μg/L based on carcinogenicity (WHO 1984).

9.2 NATIONAL

9.2.1 Regulations

Current OSHA permissible exposure limits (PEL) for tetrachloroethylene are a 100-ppm 8-h TWA and a 200-ppm acceptable ceiling concentration, with a 300-ppm maximum peak above the ceiling concentration for a maximum duration of 5 min in any 3 h.

The EPA (1985c) lists a reportable quantity (RQ) of 1 lb for tetrachloroethylene. The RQ will be raised to 100 lb in 1988. FDA (1984) lists tetrachloroethylene as a substance for use only as a component of adhesives. As an adjuvant substance used in the manufacture of foamed plastics, FDA (1984) limits its use to serving only as a blowing agent adjuvant in polystyrene at a level not to exceed 0.3% by weight of finished foam polystyrene intended for use in contact with certain types of food.

9.2.2 Advisory Guidance

9.2.2.1 Air

NIOSH designated tetrachloroethylene as a carcinogen and recommends that occupational exposure be limited to the lowest feasible limit (NIOSH 1986). ACGIH (1986) recommends a TLV-TWA of 50 ppm and a TLV-STEL of 200 ppm for tetrachloroethylene.

The upper-bound estimate of the incremental cancer risk for humans exposed for a lifetime to 1 μg tetrachloroethylene/m^3 in air ranged from 2.85×10^{-7} to 9.47×10^{-7}; this range was based on potency estimates calculated from six sets of tumor incidence data from animal studies (EPA 1986). Using the most conservative upper-bound estimate of risk, 9.47×10^{-7} $(\mu g/m^3)^{-1}$, the exposure levels associated with increased lifetime upper-bound cancer risks of 1×10^{-4} to 1×10^{-7} are 1.6×10^{-2} to 1.6×10^{-5} ppm (EPA 1986).

9.2.2.2 Water

The EPA (1987b) has developed the following guidance for water:

One-day (child)	2.0 mg/L
Ten-day (child)	2.0 mg/L
Longer term (child)	1.4 mg/L

Longer term (adult)	**5.0 mg/L**
Drinking water equivalent level (DWEL)	**0.5 mg/L**
Reference dose (RfD)	**1×10^{-2} mg/kg/day**
Lifetime health advisory (HA)	**Not recommended due to B2 carcinogenicity classification. A sample calculation was given indicating that a value of 10 µg/L would be an appropriate value if tetrachloroethylene is reclassified as a class C carcinogen.**

EPA (1980) derived cancer-based ambient water quality criteria for tetrachloroethylene. A potency estimate from the NCI (1977) bioassay was used to derive these criteria. Tetrachloroethylene levels associated with incremental increases of cancer risk of 10^{-5}, 10^{-6}, and 10^{-7} were 8.0, 0.80, and 0.08 µg/L, respectively, if exposure is assumed to be from drinking water and consuming fish and shellfish from contaminated ambient water. If exposure is assumed to be from consumption of contaminated fish and shellfish only, the corresponding criteria are 88.5, 8.85, and 0.88 µg/L in ambient water.

9.2.3 Data Analysis

9.2.3.1 Reference Dose

EPA (1987) has verified an oral RfD of 1×10^{-2} mg/kg/day for tetrachloroethylene. This value is based on a NOAEL of 14 mg/kg/day for liver effects in rats exposed to this dosage via drinking water for 90 days (Hayes et al. 1986). The RfD is calculated as follows:

$$\text{RfD} = 14 \text{ mg/kg/day}/(1{,}000) = 1 \times 10^{-2} \text{ mg/kg/day} ,$$

where 14 mg/kg/day = NOAEL
1,000 = uncertainty factor for inter- and intraspecies and subchronic-to-chronic extrapolation

This RfD supersedes an oral RfD of 2×10^{-2} mg/kg/day that was based on a NOAEL for kidney effects from an inhalation study with rats (Carpenter 1937). Further information on the derivation and use of oral RfDs is provided in Barnes et al. (1987).

9.2.3.2 Carcinogenic potency

The EPA (1986) performed quantitative carcinogenicity risk assessments for tetrachloroethylene. As detailed in the Health Effects Summary in Sects. 2.2.1.2 and 2.2.1.2, potency estimates (q_1^*) were calculated for inhalation exposure from the NTP (1986) bioassay and for oral exposure from the NCI (1977) bioassay. Using the potency estimates, the upper-bound estimate of cancer risk for exposure to 1 µg/m^3 in air ranged from 2.9×10^{-7} to 9.5×10^{-7}. The upper-bound estimate of cancer risk for exposure to 1 µg/L in water is 1.5×10^{-6}.

EPA (1986) has recommended a Group B2 (probable human carcinogen) weight-of-evidence classification for tetrachloroethylene, based on sufficient evidence from animal studies and inadequate human evidence.

EPA's Science Advisory Board has commented that a continuum between Group C and B2 may be appropriate. IARC (1987) has considered the data and given a classification of 2B (possibly carcinogenic to humans). As of January 1989, EPA has not taken a final position on the weight of evidence. Tetrachloroethylene ranks in the fourth quartile in potency compared to other compounds that the EPA considers to be carcinogenic.

9.3 STATE

Regulations and advisory guidance from the states were not available.

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11. GLOSSARY

Acute Exposure--Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Bioconcentration Factor (BCF)--The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same time period.

Carcinogen--A chemical capable of inducing cancer.

Ceiling value (CL)--A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure--Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity--The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity--Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

Frank Effect Level (FEL)--That level of exposure which produces a statistically or biologically significant increase in frequency or severity of unmistakable adverse effects, such as irreversible functional impairment or mortality, in an exposed population when compared with its appropriate control.

EPA Health Advisory--An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)--The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure--Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity--The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro--Isolated from the living organism and artificially maintained, as in a test tube.

In vivo--Occurring within the living organism.

Key Study--An animal or human toxicological study that best illustrates the nature of the adverse effects produced and the doses associated with those effects.

Lethal Concentration($_{LO}$) (LC$_{LO}$)--The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration($_{50}$) (LC$_{50}$)--A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose($_{LO}$) (LD$_{LO}$)--The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose($_{50}$) (LD$_{50}$)--The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lowest-Observed-Effect Level (LOEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

Malformations--Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level--An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen--A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity--The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

No-Observed-Effect Level (NOEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of effects seen between the exposed population and its appropriate control.

Permissible Exposure Limit (PEL)--An allowable exposure level in workplace air averaged over an 8-h shift.

q_1^*--The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD)--An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)--The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-h period.

Reproductive Toxicity--The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)--The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity--This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen--A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)--A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA)--An allowable exposure concentration averaged over a normal 8-h workday or 40-h workweek.

Uncertainty Factor (UF)--A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of humans, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX: PEER REVIEW

A peer review panel was assembled for tetrachloroethylene. The panel consisted of the following members: Dr. A. M. Guarino, University of South Alabama; Dr. James V. Bruckner, University of Georgia College of Pharmacy; and Dr. Richard R. Monson, Harvard University. These experts collectively have knowledge of tetrachloroethylene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.